ABSTRACTS

Abstracts of Papers to Be Presented at the 35th Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, March 9–13, 1986

This year, 2,985 abstracts (original contributions) were submitted for evaluation. Each was graded by eight recognized authorities in a special area of interest. Acceptance for presentation was based on the relative grade ranking in each of the 26 categories.

Ample meeting space combined with the introduction of poster sessions permitted the 1986 Annual Scientific Session Program Committee to accept 999 abstracts, approximately 33.5% of the number submitted. This represents the largest number of abstracts accepted at any Annual Scientific Session of the American College of Cardiology. Many excellent contributions were received for this year's competition, and we appreciate your support and interest.

Robert A. O'Rourke, MD, FACC
Chairman, 1986 Annual Scientific Session Program Committee

Michael H. Crawford, MD, FACC
Co-Chairman, 1986 Annual Scientific Session Program Committee

Monday, March 10, 1986
10:30AM–12:00NOON, Room #264/265/266
Intraoperative Echocardiography

ULTRASONIC INTRAOPERATIVE EVALUATION OF CORONARY LESIONS David McPherson, MD, Steve Collins, PhD, Michelle Hunt, BS, Loren Hiratzka, MD, Melvin Marcus, MD, FACC, Richard Kerber, MD, FACC, U. of Iowa, Iowa City, IA

Quantitative angiographic evaluation of coronary lesions assumes circular lumen geometry, which may not be true. Intraoperative high frequency epicardial echocardiography (HFE) allows in-vivo evaluation of coronary lesions not previously possible. We utilized HFE in 26 patients (31 lesions) undergoing CABG. Lesion shapes based on contours of the arterial lumen and wall circumference were quantified. The variability of atherosclerotic involvement was measured using the ratio of maximum (max) to minimum (min) arterial wall thickness (WT), and the % of wall circumference that had normal WT ($\leq$0.7 mm in previous studies). Residual coronary lumen shape was evaluated by measuring max/min lumen diameter (LD); shape was classified as circular (ratio $\leq$ 1.5:1); oval (>1.5:1) or complex. The location of the residual lumen within the vessel was considered eccentric if the lumen center was displaced from the vessel center by > 1 lumen radius.
Results: Max/min WT was 3.1±0.3 M±SEM (range 1.3-7.5). 16/31 lesions had ratios> 2.0, indicating varying degrees of wall involvement within individual lesions. Portions of the wall were normal in 16/31 lesions; the % normal circumference ranged from 9-85%. Max/min LD was 1.5±0.1 M±SEM (range 1.1 to 2.9). The shape of the residual coronary lumen was noncircular in 16 lesions: 13 oval, 3 complex. Seven residual coronary lumens were eccentrically placed within the vessels.
Conclusions: These data provide the first quantitative in-vivo measurements of cross-sectional coronary lesion morphology. In-vivo coronary lesions often have variable WT and noncircular lumens which are eccentrically placed. In these lesions, angiographic techniques for evaluating stenosis severity are likely to be inaccurate.

TRANS-ESOPHAGEAL REAL TIME DOPPLER FLOW IMAGING: A NEW METHOD FOR INTRAOPERATIVE CARDIAC EVALUATION. Martin E. Goldman MD FACC, Daniel Thys MD, Samuel Ritter MD, Zaharia Hillel MD PHD, Joel Kaplan MD, Mt. Sinai Medical Center, NY, NY

Intraoperative detection and quantification of valvular regurgitation or intracardiac shunt flow is difficult and inaccurate by current methods: hemodynamics and palpation. Therefore, we describe for the first time the application of intraoperative transesophageal real time Doppler flow imaging (Aloka and Irex) with a 5 MHz phased transducer mounted on a modified gastroscope. The machine superimposes a wide sector color-coded Doppler flow over a real time 2-D echocardiographic image. The tube length is 100 cm long, with 32 imaging elements spaced 0.18 mm apart, with an axial resolution of 1mm, and has a 90° image sector and 120° anterior-posterior flexibility.

Patients with valvular regurgitation, stenosis or intracardiac shunts were evaluated. In each patient the probe was easily passed into the esophagous, positioned behind the left atrium, and quickly demonstrated the abnormal flow in several views: 4 chamber, long or short axis. The presence and severity of abnormal flow was easily recognizable and estimated based on the total area of abnormal colored flow compared to the size of the entire chamber (i.e., the LA in mitral regurgitation) and correlated well with catheterization findings. Also, changes in the regurgitant or shunt flow due to variations in anesthetic agents and arrhythmias were clearly visible on line in the operating room.

Thus, transesophageal real-time Doppler flow imaging is superior to present methods for detection of abnormal blood flow in the operating room because it is rapid, reproducible and allows detection of beat to beat changes in flow patterns. Real time Doppler flow can evaluate the presence and severity of abnormal cardiac flow both before and immediately following a surgical procedure to detect its adequacy in the operating suite, potentially reducing surgical morbidity and mortality.

COLOR DOPPLER FLOW MAPPING FOR INTRAOPERATIVE ASSESSMENT OF VALVULOPLASTY AND REPAIR OF CONGENITAL HEART DISEASE.

Gerald Maurer, MD, FACC; Lawrence Czer, MD, FACC; Michele De Robertis, RN; Aurelio Chaux, MD, FACC; Robert Kass, MD, FACC; Myles Lee, MD, FACC, Jack Matloff, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA

To study the usefulness of intraoperative (OP) Doppler color flow mapping (CFM) as an early predictor for the success of cardiac surgical repair procedures, and to compare the grading of valvular regurgitation to angiography and closed chest CFM, we performed OP CFM in 35 pts. The transducer was placed directly on the epicardium before and immediately after cardiopulmonary bypass; in addition, closed chest pre- and post-operative CFM was done. Seven valvuloplasty procedures were studied: 2 for ischemic mitral regurgitation (MR), 2 tricuspid annuloplasties, 2 cleft mitral valve repairs and 1 cleft tricuspid valve repair. OP CFM showed that in 6 of the 7, regurgitation decreased from severe (3 or 4+) to none or trace. One mitral valve was found to be insufficient (3+) at the residual cleft. Postoperative CFM and physical examination confirmed these findings early (pre-discharge) as well as in subsequent follow up. The adequacy of shunt closure of secundum (4) and primum ASD (2), VSD (2), patent foramen ovale (2) and the atrial redirection of flow in Mustard procedure for d-transposition (1) were clearly confirmed. In 15 pts with St. Jude valve replacements (7 mitral, 5 aortic, 3 double) mild prosthetic valve regurgitation and 3 separate antegrade flow jets were demonstrated. Seven control pts with CABG and no valve surgery were also studied. In all groups, severity of MR and aortic regurgitation by OP CFM corresponded well to angiography and closed chest CFM.

CONCLUSION: OP CFM appears to be a powerful intraoperative predictor of the outcome of valvuloplasty and congenital repair procedures and may thus prevent the need for later reoperation.

THE INTRAOPERATIVE DETECTION OF MYOCARDIAL INFARCTION BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Bruce Shively, M.D., Thomas Watters, M.D., David Benefiel, M.D., Michael Canalan, M.D., Elias H. Botvinick, M.D., F.A.C.C., Nelson B. Schiller, M.D., F.A.C.C., University of California, San Francisco, CA

We assessed the value of transesophageal echocardiography (2D-TEE) for detection of intraoperative myocardial infarction (MI) in 57 patients (pts) undergoing coronary bypass surgery. During the first 24 hrs postop all pts had ≥2 EKG's and ≥1 CKMB and infarct-avid imaging with Technetium 99m-Imidodiphosphonate (IDP) 3-7 days postop. Wall motion on serial intraop 2D-TEE recordings was scored in each of 4 quadrants of the LV short axis view. Final scores required agreement by 2 of 3 observers blinded to other test results. 2D-TEE was ⊕ for MI if a normal region became hypo- or akinetic or if a hypokinetic region became akinetic. 2D-TEE was ⊖ for MI if regional wall motion showed transient or no change. Pts with any 2 of 3 tests ⊕ (EKG, CKMB, or IDP) were considered ⊕ for MI. 6 pts with the first ⊕ CKMB > 24 hrs postop were excluded. Table 1 shows that for detection of MI 2D-TEE had a sensitivity of .46, specificity of .95, ⊕ predictive value of .75 and ⊖ predictive value of .84. If pts with baseline severe diffuse hypokinesis are excluded, the number of false ⊖ 's decreases from 7 to 4. Table 2 shows relative agreement of EKG and 2D-TEE with MI (⊕ IDP and ⊕ CKMB). The frequency of agreement of 2D-TEE with MI is > EKG with MI. Table 3 shows high agreement of IDP and 2D-TEE with MI (⊕ EKG and ⊕ CKMB). 2D-TEE shows promise for immediate postop detection of MI in this high risk group when EKG is the only other available test. The sensitivity of 2D-TEE is higher in pts without severely decreased baseline systolic function.

2D-TEE \ MI	⊕	⊖
⊕	6	2
⊖	7	36

Table 1

2D-TEE \ EKG	agree	dis-agree
agree	33	6
dis-agree	2	3

Table 2

2D-TEE \ IDP	agree	dis-agree
agree	37	3
dis-agree	2	2

Table 3

INTRA-OPERATIVE ECHOCARDIOGRAPHIC EVALUATION OF THE TEXTURE OF THE ISCHEMIC MYOCARDIUM.

K. Chandrasekaran, M.D., J. F. Greenleaf, Ph.D., K. H. Kim, M.D., B. S. Robinson, Ph.D., W. D. Edwards, M.D., F.A.C.C., J. B. Seward, M.D., F.A.C.C., and A. J. Tajik, M.D., F.A.C.C., Mayo Clinic, Rochester, MN

The effect of variable periods of reversible ischemia (Is) on 2D echo (2DE) texture (Tx) of the myocardium (M) was evaluated from 2DE obtained intra-operatively in 9 dogs using a high-frequency (Hf) 12 MHz ultrasonic scanner to determine whether it can identify Is M from normal. 2DE of anterior (Aw) and posterolateral (Pw) walls of left ventricle were obtained in the control state (C), and at 5, 15, and 30 mins (') of Is produced by ligation of left anterior descending coronary artery. 8-bit gray level values for backscatter amplitude (Bs) were obtained from digitized video images. Aw thickness (t) decreased during systole (S) and diastole (D) at 5' of Is compared to C. No further changes occurred at 15' and 30' of Is. t in mm at C were S=6.8±2.2 and D=4.4±1.2 and at 5' of Is, S=3±0.5 and D=2.4±0.6. 2DE of Aw subjected to Is, revealed increased brightness compared to C and normally perfused Pw. Mean gray level values ($\bar{x}$±SD) of Bs from Aw and Pw were:

	#	Aw(S)	Aw(D)	#	Pw(S)	Pw(D)
C	9	40.3±37.7	72.6±47.6	8	38.3±25.1	66.6±39.0
5'	7	66.1±46.0*	67.4±33.9†	6	28.0±11.2	52.5±34.5
15'	8	97.5±51.4*	88.6±54.2†	7	39.6±23.3	69.3±38.9
30'	8	101.5±45.6*	95.7±40.1†	7	40.3±23.6	74.4±43.4

(P*<0.0001, †P<0.05 compared to C)

We conclude: Hf 2DE revealed abnormal Tx of Is M which could be confidently differentiated from normal M. Gray level values significantly increased in Is M as early as 5', thereby providing a potential means of reliably recognizing Is M intra-operatively.

THE CONTINUOUS WAVE DOPPLER ESOPHAGEAL PROBE: A NEW METHOD FOR MEASUREMENT OF CARDIAC OUTPUT DURING SURGERY

Anil Kumar, MD, S Minagoe, MD, D Thangathurai, MD, M Mikhail, MD, D Novia, MD, J Viljoen, MD, PAN Chandraratna, MD, FACC, SH Rahimtoola, MD, FACC. LAC-USC Medical Center, Los Angeles, CA

In 14 patients (pts) with cardiopulmonary disease cardiac output (CO) was measured during surgery with a new continuous wave doppler (CWD) transducer positioned in the esophagus. The ultrasound beam interrogates descending aortic flow at 45°. The transducer was connected to a modified Ultracom Cardiac Output Monitor and blood flow velocity in descending aorta (DAV) was measured. Doppler cardiac output (DCO) was determined by the relationship DCO=K.DAV, where K is a derived constant based on ascending aortic diameter and a simultaneous measurement of blood flow velocity in ascending aorta from a suprasternal probe and the DAV. CO was also measured by thermodilution technique (TDCO). TDCO and DCO measurements (n=246 in 14 pts) temporally close were averaged & arranged into epochs (n=84). Mean TDCO was 5.90±3.27 (±SD) l/min & mean DCO was 6.21±4.0/min for the whole group (r=.76; SEE=1.76 l/min). Trends in TDCO were reliably paralleled by DCO except at very high CO values. Adequate Doppler signal was unobtainable in 1 pt; frequent transducer repositioning was needed in another. No untoward effects were noted. Reproducibility studies in 8 other pts showed good interobserver (mean difference .41±.36 l/min) and intraobserver (mean difference .64±.52 l/min) reproducibility. DCO measurement by CWD esophageal probe is a noninvasive method for measuring CO during surgery in high risk pts with cardiopulmonary disease.

Monday, March 10, 1986
10:30AM-12:00NOON, Room #260/261
Clinical Cardiac Pacing

DISCRIMINANT P WAVE SENSING ABOLISHES ENDLESS LOOP TACHYCARDIA

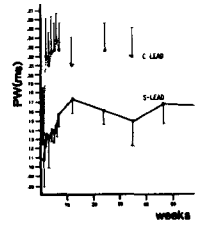
Peter T. Klementowicz, M.D., Seymour Furman, M.D., F.A.C.C.
Montefiore Medical Center, Bronx, New York

Adequate atrial sensing depends upon several features of the atrial signal: amplitude, slew rate and frequency content. With the introduction of dual chamber pacemakers which have multiple atrial amplitude sensing values, selective P wave sensing is possible. Antegrade atrial signals can be sensed while smaller retrograde signals are ignored. To demonstrate the clinical utility of selective P wave sensing we studied 5 consecutive pts who had 1) retrograde conduction 2) antegrade atrial signals which were at least 1.4 times larger than their corresponding retrograde atrial signals and 3) dual chamber pulse generators which are capable of discriminating this difference in atrial amplitude. Each pt was programmed to the DDD mode and the postventricular atrial refractory interval was at least 100 ms shorter than the individual's minimal retrograde conduction time. Two atrial sensitivity settings were evaluated in each pt: a high setting to ensure sensing of both antegrade and retrograde P waves and a lower setting to allow sensing of antegrade P waves only. Ambulatory Holter monitoring demonstrated that with a high sensitivity setting each pt sustained endless loop tachycardia (mean # of episodes 41, range 6 to 143) and that a low atrial sensitivity setting eliminated the tachycardia. With the lower atrial sensitivity setting, there was only sporadic atrial undersensing (1.5 episodes for each 1000 P waves). Conclusions: This study demonstrates that atrial signals having different amplitudes can be selectively sensed. Also, dual chamber pulse generators with mulitple atrial amplitude sensitivity values can discriminate antegrade from retrograde P waves, ensure antegrade sensing, reject retrograde P waves and eliminate endless loop tachycardia.

THE LATE EFFECTS OF STEROID-ELUTING LEADS

Gerald C. Timmis, M.D., F.A.C.C., Victor Parsonnet, M.D., F.A.C.C., Seymour Gordon, M.D., F.A.C.C., Douglas C. Westveer, M.D., F.A.C.C. and James R. Stewart, M.D., F.A.C.C., William Beaumont Hospital, Royal Oak, Michigan and Beth Israel Medical Center, Newark, New Jersey.

Previous reports have compared the performance of steroid-eluting leads (S-lead; Medtronic 4003) to that of conventional leads. This study contrasts chronic thresholds resulting from elution of dexamethasone-sodium phoshate to those of identically configured control leads with platimum-coated porous titanium electrodes but no steroid (C-lead; 10176). Twenty of 28 patients with the S-Lead and 6 of 14 with the C-Lead were followed for 18 months to determine whether prevention of early threshold peaking and subsequent lowering of thresholds is sustained by the S-Lead. Serial pulse width (PW) thresholds at one quarter generator output (1.35 V) were measured each week (wk) x 6 and every three months (mo) thereafter, using a Medtronic 5907C programmer-receiver. A plot of serial thresholds (ms) is depicted. While no threshold peaking occurred with either lead, PW thresholds (ms) were substantially lower at 18 months (p=.023, ANOVA) with the S-Lead (.15±.05) than the C-Lead (.27±.004). No exit block was seen with S- or C-Leads. This suggests that early steriod-suppression of inflammation and/or fibrosis chronically increases effective current density and/or lowers pacing impedance.



CONCLUSIONS: Chronic thresholds with S-Leads are consistently lower than those of C-Leads. To improve generator longevity current drain can be programmed to its lowest level with S-Leads which are also ideal for managing high threshold problems.

THE EFFECTS OF NUCLEAR MAGNETIC RESONANCE (NMR) ON IMPLANTABLE PULSE GENERATORS

David L. Hayes, M.D., F.A.C.C., David R. Holmes, Jr., M.D., F.A.C.C., Joel E. Gray, Ph.D., Joseph G. Fetter*, George C. Aram*, Peter Tarjan, M.D.**, Lisa Prechter**, Mayo Clinic, Rochester, MN; * Medtronic, Inc., Minneapolis, MN; and ** Cordis Corporation, Miami, FL.

Whether all patients with permanent pacemakers should be restricted from NMR studies has not been established. This study assessed the effects of an NMR imager operating at 1500 gauss and 6.4 megahertz on 5 single and 9 dual-chamber pacemakers from 5 manufacturers in the VVI, AAI, DDD and VDD modes. Pacemakers were implanted and connected to leads in an anesthetized dog placed in the NMR radiofrequency field which was pulsed at 200, 300, and 1000 pulse/minute rate with a maximum power of 1000 watts. The dog was connected to ECG telemetry and femoral intra-arterial pressure monitoring. All pacemaker reed switches closed producing asynchronous pacing as they were brought into the static magnetic field. Four single and 4 dual-chamber pacemakers paced the heart at the radiofrequency pulse period resulting in rates to 300/min and concomitant fall in intra-arterial pressure. Phantom programming was not observed. Two pacemakers did display transient complete inhibition following a period of radiofrequency exposure.
Summary: The mechanism of this rapid pacing at the radiofrequency pulse period is not completely understood. Although it appears that patients with implanted pulse generators not affected during our tests may undergo NMR scans of comparable field strengths, other pulse generators and NMR units of greater field strengths must be evaluated before any comprehensive recommendation can be made.

PHYSIOLOGIC PACING BASED ON BEAT-TO-BEAT MEASUREMENT OF RIGHT VENTRICULAR dP/dt MAX: INITIAL FEASIBILITY STUDIES IN MAN.

Arjun Sharma, M.D., F.A.C.C., Richard Sutton, M.D., F.A.C.C., Tom Bennett, Ph.D., George Klein, M.D., F.A.C.C., Kenneth Anderson, Robert Beck, London, Canada; London, England; and Minneapolis.

Recent studies in a canine model of heart block indicate that pacing rates controlled by right ventricular (RV) dP/dt max may closely approximate the rate response to atrial synchronous pacing (VAT). We examined the feasibility of using this new modality to provide physiologic pacing in man. Four patients (age 31-84) with complete heart block were studied. A permanent ventricular endocardial pacing lead (Medtronic 6220) which incorporates a dynamic pressure sensor was implanted with a VVI pacemaker (Medtronic 2451). RV pressure was non-invasively monitored by telemetry at times between 3 and 18 months post implant. The patients underwent treadmill exercise testing and postural changes during VVI pacing at rate 70. This data was used to determine the relationship between dP/dt max and pacing rate. Patients underwent repeat treadmill testing with the RV pressure wave form computer processed on a beat-to-beat basis. The computer emitted pulses at a variable rate proportionate to RV dP/dt max, and the amplified pulses were used to drive the pacemaker in the triggered mode. In this mode of pacing increases in rate were observed with increased exercise levels (Δ HR+29.3±5.4 bpm at peak exercise). Rate increased with active postural change (+ 12 bpm) and passive tilt (+ 11.3 bpm). We conclude that physiologic pacing based on RV dP/dt max is a feasible alternative to present modalities.

RESPIRATION RELATED INTRAVASCULAR IMPEDANCE CHANGES AS A RATE CONTROLLER FOR CARDIAC PACING. Tony Simmons MD, James Maloney MD, Freddy Abi-Samra MD, Harry Valenta PhD, Tibor Napholtz, PhD, Lon Castle MD, Victor Morant, MD. Cleveland Clinic Fndn., Cleveland, OH

The need for a cardiac pacemaker responsive to metabolic demand is well accepted, but the methods to monitor metabolic demand have been deficient. A new method is described which uses intravascular impedance (IImp) changes to monitor respiratory (Resp) rate and tidal volume. A potential advantage of this method is that a permanent pacing system would require only minor modifications of standard pacing leads.

Employing standard multipolar catheters nine patients had unipolar and bipolar IImp measurements using multiple sites [SVC, pectoral skin (SK), and endocardial and free-floating RA and RV sites] as the stimulating and sensing electrodes. The current source was a 1 mAmp, 33 μsec, 90 Hz signal. The amplitudes of both the Resp and stroke volume (SV) components of the IImp were measured. The ratio of maximal forced ventilation (MFV) to normal breathing (nasal thermistor) was used as an index of sensitivity; the ratio of the Resp to the SV components was used as an index of specificity.

IImp changes reflecting Resp rate, tidal volume and SV were accurately determined in all patients. The average IImp during normal Resp and during MFV for all configurations studied were 0.37 ± 0.34 and 1.23 ± 1.07 ohms, respectively. The SV component varied from 0.2 to 0.35 ohms depending upon electrode sites. The best combination of sensitivity and specificity was obtained by stimulating from the free-floating RV and SK sites and sensing from the free-floating RA and SK sites. This produced sensitivity and specificity ratios of 6 and 13, respectively.

Thus, Resp rate and tidal volume measurements using IImp with multipolar catheters in the SVC and cardiac chambers are technically feasible and may provide a new method suitable for use as a rate controller for cardiac pacing.

BIPOLAR PACING THRESHOLDS BETWEEN A SINGLE MYOCARDIAL ELECTRODE AND EPICARDIAL PATCH ELECTRODE ARE SUPERIOR TO THOSE BETWEEN TWO MYOCARDIAL ELECTRODES. Paul J. Troup, M.D., F.A.C.C., Jule N. Wetherbee, M.D., Peter D. Chapman, M.D., Gordon N. Olinger, M.D., Medical College of Wisconsin, Milwaukee, Wi.

To determine the feasibility of pacing from 1 of the shocking leads of the automatic implantable cardioverter defibrillator (AICD), we compared pacing data between 2 Intec Model K-54 myocardial screw-in electrodes (MSEs) and those between 1 of the MSEs and a ventricular [13.5 cm^2 (11 patients) or 27 cm^2 (32 patients)] patch shocking electrode placed over the anterior or posterolateral left ventricle in 43 patients undergoing AICD lead system implants. The pacing threshold data were as follows:

	2 MSEs	MSE to Patch
Voltage Threshold	1.90±1.2 volts	1.06±0.77 volts*
Current Threshold	3.30±2.4 mA	3.32±3.0 mA
Resistance	640±150 ohms	383±131 ohms*
Electrogram Amplitude	12.43±5.8 mV	13.05±5.8 mV

* = p <0.01.

There was no significant voltage threshold difference between the 13.5 cm^2 and 27 cm^2 patch employed as the pacing anode. We conclude that voltage threshold and resistance are significantly reduced by pacing between a myocardial lead and patch electrode without compromising electrogram amplitude when compared with pacing between 2 MSEs. A greater safety margin for ventricular capture may be provided in patients with future generation AICDs employing the patch electrode for pacing.

Monday, March 10, 1986
10:30AM-12:00NOON, Room #360/361
Thallium 201: I. Quantitative Methods and Dipyridamole Studies

PROGNOSIS IN CORONARY ARTERY DISEASE: ASSESSMENT BY QUANTITATIVE STRESS-REDISTRIBUTION Tl-201 MYOCARDIAL SCINTIGRAPHY. Jamshid Maddahi, MD, FACC; Joshua Gurewitz, CNMT; Timothy Bateman, MD, FACC; Howard Staniloff, MD, FACC; Ishac Cohen, PhD; Daniel Berman, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA

We have previously shown with quantitative stress-redistribution Tl-201 studies (Q-Tl) that the presence of perfusion defect (PD) and/or slow washout (SW) in the distribution of left-main (LM) and/or all three coronary arteries (TVD) identifies high-risk angiographic CAD. Thus, we assessed whether different patterns of PD and SW could predict subsequent coronary events in 1022 patients who underwent stress-redistribution Q-Tl imaging from July 1980 to July 1982. Of 86 pts suffering a coronary event at 1 year followup, 13 had cardiac deaths, 27 nonfatal myocardial infarctions (MI), and 46 worsening of symptoms requiring late bypass surgery (LCABG) (>60 days after Q-Tl). In the 769 without and 253 with prior MI, the prognostic significance of 3 Q-Tl patterns were assessed: I) normal, II) abnormal but without, and III) with PD and/or SW in TVD or LM distribution. Event rates (%):

			Death	MI	LCABG	Total
No Prior MI	I	(n=481)	0.2	0.8	2.3	3.3
	II	(n=232)	2.1	1.7	6.0	9.8
	III	(n= 56)	3.6	7.1	8.9	19.6
With Prior MI	I	(n= 54)	1.8	3.7	1.8	7.3
	II	(n=126)	1.5	5.5	5.5	12.5
	III	(n= 73)	2.7	8.2	10.9	21.8

SW abnormality was responsible for placing 7/11 no prior MI pts with events and 4/6 prior MI pts with events into Group III. Conclusion: 1) different patterns of PD and SW by Q-Tl are predictive of 1-year coronary events in patients with and without prior MI and 2) quantification of SW adds to the prognostic abilility of PD alone.

"SILENT" EXERTIONAL ISCHEMIA IN PATIENTS WITH HIGH-RISK CORONARY ARTERY DISEASE. Steven Reisman, MD; Jamshid Maddahi, MD, FACC; Alan Rozanski, MD; Daniel Berman, MD, FACC. VA Medical Center, Long Beach, and Cedars-Sinai Medical Center, Los Angeles, CA

In light of recent reports suggesting a high frequency of asymptomatic ("silent") ischemia in patients with coronary artery disease (CAD), increasing attention is being focused on the clinical importance of chest pain symptomatology in patients with "high-risk" CAD, defined as left-main and/or triple-vessel CAD. Since the results of testing influence clinical decisions in this group, we analyzed the relationship between the presence or absence of exertional angina during treadmill testing and the extent and severity of exercise-induced ischemia, by evaluating 55 consecutive patients (pts) with Tl-201 exercise-induced ischemia (≥1 reversible segment) and left-main and/or triple-vessel stenosis (≥50%). Three-view Tl-201 scintigrams were divided into 15 segments. Severity of exercise-induced ischemia was represented by a Tl-201 ischemic severity score (ISS) and extent of ischemia by # reversible Tl-201 segments. Exertional angina during treadmill testing was present in 34 pts (62%) (GpI) and absent in 21 pts (38%) (GpII).

	ISS	# R Segs	Ex Dur	HR	Max ST↓
GpI	7.1±4.6	4.2±2.5	6.8±2.5	134.7±22.9	2.0±1.5
GpII	6.7±4.0	4.0±2.0	7.9±3.3	137.4±18.4	2.4±1.1

R segs=reversible segments; Ex=exercise; Dur=duration (minutes); HR=peak heart rate; Max ST↓= maximum ST depression (mm). No significant differences were noted between the two groups. We conclude that in pts with high-risk CAD and Tl-201 ischemia, silent exertional ischemia is common and does not indicate a less ischemic group. Thus, the presence or absence of angina during treadmill testing may not be reliable for guiding medical or surgical intervention in this patient group.

QUANTITATIVE SUBTRACTION THALLIUM-201 IMAGING TO ASSESS THE EFFECTS OF ACUTE REPERFUSION IN MYOCARDIAL INFARCTION

Robert C. Bourge, M.D.; Russell C. Reeves, MD, FACC; William J. Rogers, MD, FACC; Patrick L. Whitlow, MD, FACC; Joseph R. Logic, MD; Michael V. Yester, Ph.D; Gerald M. Pohost, MD, FACC. University of Alabama, Birmingham, Alabama.

We applied a new computerized subtraction program to myocardial Tl-201 images obtained prior to and immediately after intracoronary streptokinase and/or coronary angioplasty in 16 male patients with acute myocardial infarction (age=49.1±8). Reperfusion by either method was demonstrated in 13 of 16 patients 5.7±1.3 hr after onset of pain. Prior to intervention early images (E) were obtained 10 min after 1 mCi of Tl-201 IV, in the anterior and 45°LAO views. After intervention, "mask" images were obtained, an additional 2 mCi given, and repeat images were obtained. The subtraction program aligns the mask and repeat images in each view and produces a "subtracted" image (S) representing Tl-201 distribution after the 2 mCi dose. Delayed images (D) were obtained 2 hr later. A gated radionuclide angiogram was then performed and repeated 7 days post MI. All thallium images were quantitatively analyzed resulting in an index of thallium activity for each of 15 segments in each view normalized to the segment with the most activity in E. The Tl-201 activity in segments with decreased activity in E (<60% of the maximum activity) were compared to these same segments in S and D and the differences summed to obtain a value comparing images in each patient. Patients with improvement in global ejection fraction > 5 units had increased Tl-201 activity in S compared to E (S-E = 9.2±4), significantly higher than patients with no significant change in ejection fraction (S-E = 2.7±6; p<.05). No significant difference was found in D-E activity between groups. We conclude that quantitative subtraction Tl-201 imaging may permit early prediction of myocardial salvage (as evidenced by improvement in myocardial function) with acute reperfusion in myocardial infarction.

QUANTITATIVE ASSESSMENT OF DIPYRIDAMOLE THALLIUM-201 PLANAR SCINTIGRAMS: COMPARISON OF DIPYRIDAMOLE-SPECIFIC TO STRESS NORMAL LIMITS.

George T O'Byrne, MB; Daniel Berman, MD, FACC; Kenneth Van Train, BS; John Friedman, MD; David Ramsdale, BA; Alan Rozanski, MD; Jamshid Maddahi, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA

Since visual interpretation of dipyridamole (dipy) thallium-201 (Tl) is subjective, we developed an objective technique for identification of initial defects or slow washout abnormalities from dipy Tl studies and evaluated 34 patients (pts) (19 catheterized CAD pts and 12 with a <1% likelihood of CAD). Following 0.56 mg/kg dipy and hand-grip exercise, Tl and subsequently aminophylline were injected intravenously. Three-view, 10-minute images were obtained at 5 minutes and 4 hours after dipy. Following interpolative background subtraction and 9-point smoothing, initial distribution and % washout circumferential profiles in each pt were compared with the lower limit of normal (nl) derived from the low-likelihood dipy pts. For comparison, CPs were also compared to previously developed stress and washout nl limits from low-likelihood pts having stress Tl. Abnormality was defined by ≥2 18° arcs falling below nl limits. Results:

	CAD	LAD	LCX	RCA	TOTAL VESSELS
Sens & (Spec)	89%	76%	46%	92%	73%
c̄ Dipy Nl Limits		(62%)	(78%)	(78%)	(73%)
Sens & (Spec)	89%	76%	85%	92%	85%
c̄ Stress Nl Limits		(12%)	(44%)	(57%)	(35%)

Sens=sensitivity, Spec=specificity. True negative rate in low-likelihood nls was 10/11 (91%) for the dipy nl limits vs 5/12 (42%) using stress nl limits. Thus, nl limits for objective, computerized analysis of Tl images must be procedure specific: nl limits from stress pts for dipy Tl studies result in unacceptably low specificity. Dipy-specific nl limits result in accuracy similar to that previously seen in quantitative analysis of stress Tl studies.

DIPYRIDAMOLE THALLIUM IMAGING UNMASKS EVIDENCE OF ISCHEMIA IN PATIENTS WITH NORMAL BUT SUBMAXIMAL EXERCISE THALLIUM TEST

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False negative exercise thallium scans occur when the level of exercise was submaximal and the perfusion abnormality was not unmasked. To study the incidence of this problem, we evaluated the ability of non-exercise stress thallium imaging following intravenous dipyridamole to detect ischemia in patients with normal but submaximal exercise thallium tests. In a prospective study of 385 consecutive exercise thallium tests, 72 (19%) were judged to be normal submaximal tests after meeting the following criteria: (1) maximum heart rate achieved <85% of the heart rate predicted based on age and/or shortened treadmill time and (2) absence of angina, diagnostic ST-segment depression and thallium redistribution. Twenty-one patients consented to return for dipyridamole thallium imaging within a mean period of 18 days. Six (29%) of these demonstrated thallium redistribution with dipyridamole thallium imaging that was not present during exercise thallium imaging. Mean age (57 vs 53 years), maximum heart rate achieved (135 vs 134 bpm), treadmill time (5.5 vs 7.2 min) and history of previous myocardial infarction (2 vs 5) were similar (P=NS) in those with and without redistribution.
We conclude (1) normal submaximal exercise thallium tests occur commonly in an active nuclear cardiology laboratory and (2) dipyridamole thallium imaging unmasks evidence of ischemia in more than 25 percent of such cases.

INABILITY OF PLANAR THALLIUM SCINTIGRAPHY TO PREDICT 50% DECREASE IN CORONARY VASODILATOR RESERVE.

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Previous validation studies of thallium scintigraphy (TS) have relied almost entirely on percent stenosis (%S) measurements from coronary angiograms. To validate TS with a more sophisticated gold standard, we assessed coronary vasodilator reserve (CVDR) in individual vessels with a unique coronary Doppler catheter before and after intracoronary Papaverine. In 18 normals, CVDR assessed by measuring peak-to-resting flow velocity was 5.1±0.6 (range 3.7-8.2). We measured CVDR in 13 stenosed vessels of patients with primarily single-vessel disease (3 LAD; 5 LCx; 3RCA; 2 double vessel) and normal left ventricular function. %S varied from 20% to 95%. Within 14 days of the physiologic study, TS was performed utilizing intravenous dipyridamole. TS planar images were interpreted by 3 experienced readers who were blinded to any clinical data. As expected, in the study group (N=6) with normal CVDR (4.68±.30, mean±SEM) all scintigrams were normal. Surprisingly, in the 7 with low CVDR (2.47±.22) no TS defects were detectable. In a previous study in patients with multivessel coronary disease (N=51) planar dipyridamole TS had a sensitivity of 80%. These preliminary data suggest that planar TS with dipyridamole cannot reliably detect coronary obstructive lesions associated with a 50% decline in CVDR. Studies in additional patients will be needed to determine the decline in CVDR that can be detected with TS.

Monday, March 10, 1986
10:30AM–12:00NOON, Room #366/367
Accessory A-V Connections

THE VALUE OF THE RESTING 12 LEAD ECG FOR LOCALIZING THE SITE OF PREEXCITATION IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME: DISCREPANCY WITH PREVIOUS OBSERVATIONS. Lemery R, Hammill SC, Holmes DR, Mankin HT, Danielson GK, Gersh BJ, Wood DL, Osborn MJ, Mayo Clinic, Rochester, MN.

Criteria for localizing an accessory pathway(AP) have been established using the 12 lead ECG (World Health Organization criteria, Ref 1) and using maximal preexcitation during atrial pacing (Duke criteria, Ref 2). To determine the usefulness of both sets of criteria,we reviewed 47 pts who had a single antegrade conducting AP at the time of surgical ablation. The delta wave was analyzed on the resting ECG comparing with Ref 1 & 2: exact concordance (EC), best predictors (BP) and worst predictors (WP) of AP location. Results were not affected by QRS width (< or > 120 msec).

AP	No.	Delta wave Ref 1			Delta wave Ref 2		
Loc	Pts	EC	BP	WP	EC	BP	WP
Left Lat.	18	3	+V_1 ±V_6 +QRSIII	Q-QS I,V_6 -V_6	1	+V_1-V_4, +/-V_6	+II,III,F -V_6,-+-V_5
Left Post.	13	0	+V_1 +QRS V_1	-+V_6 -QRSIII	0	+V_1-V_4 +V_5	-II,III,F - +/-V_6
Post. Para-Septal	9	0	-II,III, -F,+I	+V_2-V_6 rSV_1,RsV_2	L 1	+V_1-V_4, -II,III,F	+V_6
					R	-II,III,F +V_2	+I,L,V_4-6 +/-V_1
Right Post.	3	0	Q,QSIIIF -QRSIIIV$_1$	-V_1	0	+I,L,V_4-6 +V_3,+/-+V_1	-II,III,F +/-V_2
Right Lat.	4	0	-QRSIIIV$_1$ +I	±V_1	0	+I,L,V_4-6	-+II,IIIF +/-V_2
Total	47	3/47			2/47		

In conclusion: in this group of pts. using criteria established in Ref 1 & 2, the 12 lead ECG rarely predicted the exact location of the AP.

PATTERNS OF RETROGRADE HIS PURKINJE SYSTEM BLOCK INITIATING ORTHODROMIC TACHYCARDIA WITH VENTRICULAR PACING IN THE WOLFF PARKINSON WHITE SYNDROME. Patrick Tchou, MD, Mohammad Jazayeri, MD, Issam Al-Bitar, MD, Rehan Mahmud, MD, FACC, Stephen Denker, MD, FACC, Michael H. Lehmann, MD, FACC and Masood Akhtar, MD, FACC, Univ. of WI Mt. Sinai Med Center, Milwaukee, WI

Using a specially designed pacing protocol, the manner in which the orthodromic tachycardia (OT) induction is achieved during constant cycle length incremental ventricular pacing (VP) was systematically studied in 16 patients with Wolff Parkinson White syndrome (WPW). A train of VP (S_2S_2) was initiated after a programmable interval (S_1S_2) following a controlled atrial drive (S_1S_1). The number of beats in the S_2 train was progressively increased from 1-8 beats and the retrograde response of His Purkinje system (HPS), accessory pathways (AP) and the AV node was separately analyzed for each beat of the S_2 train. Results: In all patients a retrograde block in the HPS appeared essential to initiate the OT. However, three distinct patterns of HPS block preceded the OT induction. In 11/16 the block of second or the third beat (retrograde Wenckebach HPS) initiated OT. When OT induction was delayed beyond the third beat of S_2 train two other patterns preceded the OT onset. In 2/16 a 2:1 retrograde block occurred in the HPS and AP until the 4th beat which conducted via the AP only, and started the OT. Remaining three cases demonstrated a Linking phenomenon in the HPS for extended period of time beyond the third beat. During Linking an anterograde migration in the site of block preceded the initiation of OT. These data illustrate that the onset of OT with VP involves complex electrophysiologic mechanisms and emphasize the importance of a beat by beat analysis for establishing the precise mechanism of OT initiation during VP in the WPW syndrome.

DIFFERENCES BETWEEN TRUE AND FALSE LINKING IN PATIENTS WITH ACCESSORY PATHWAYS

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Lehman et al presented a variety of examples where the unifying theme reflected that each impulse entering a macroreentry circuit was functionally linked to the sequelae of the previous impulse in a way capable of producing repetitive functional block. To evaluate linking (L), that is, the mechanisms of perpetuation of functional anterograde(A) block in an accessory pathway(AP),electrophysiologic studies were performed in 12 patients(pts) with manifest Wolff-Parkinson-White syndrome who had: a) bidirectionally-conducting AP with fusion QRS complexes during sinus rhythm and narrow ventricular beats during reciprocating tachycardia(RT); and b) 1:1 AV conduction at similar cycle lengths through the normal pathway, as well as via the AP. In 11/12 pts, L was maintained by interference when atrial stimulation(AS) was started during sinus rhythm because each new A impulse was blocked (within the AP) by the refractoriness produced by the retrograde(R) concealed penetration of the previous impulse and every R impulse was blocked by the refractoriness engendered by the concealed A impulse. The latter also prevented initiation of RT upon the cessation of AS. On the other hand, when AS was initiated during RT, L was sustained by collision within the AP and was followed by resumption of the RT upon stopping AS(entrainment).Finally, when 1:1 conduction took place via the AP, the level (within the normal pathway) at which this "reversed" L occurred could not be determined. To summarize: 1) both L and "reversed" L are maintained by interference, but when collision is the sustaining cause, the phenomenon is not true L, but a separate mechanism, namely entrainment.

TACHYCARDIAS ORIGINATING IN ACCESSORY PATHWAY NETWORKS MIMICKING ATRIAL FLUTTER AND FIBRILLATION

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We have shown that accessory AV pathways(AP) may function as a meshwork of branching fibers, with some branches not electrically connected to the atrium, ventricle or both. These isolated networks could theoretically support reentry. In 3 pts, a rapid, irregular tachycardia was associated with nearly continuous electrical activation in the AP apparatus. Changes in the timing of key AP potentials were followed by similar changes in the timing of atrial activation. Block within the pattern of continuous activation was followed by termination of the tachycardia. In pt 1 with a concealed left paraseptal AP and pt 2 with an overt left anterior AP, AP potentials were recorded along the coronary sinus for distances of 6 mm and 20 mm, respectively, using closely spaced orthogonal electrodes and low recording gain. AP tachycardia was induced by programmed atrial stimulation. Retrograde atrial activation produced discrete P waves simulating atrial flutter in pt 1. Rapid, irregular preexcited QRS complexes masked P waves and mimicked atrial fibrillation in pt 2. Mean tachycardia cycle length (CL) in pt 1 was 180 msec with 110 msec continuous AP activity through the 80 msec isoelectric period between P waves. In pt 2, mean tachycardia CL was 185 msec. Continuous electrical activity was present near the ventricular insertion of the AP while the atrial insertion of the AP and local atrium were activated in the same sequence as during ventricular pacing. In pt 3 with an overt right anterior AP, numerous interrelated AP potentials were recorded over a 15 mm segment of the tricuspid anulus from 2 mm spaced bipolar electrodes on an octapolar catheter positioned against the tricuspid anulus, parallel to the His bundle catheter. AP tachycardia was induced by rapid ventricular pacing during oral encainide therapy and had mean CL 310 msec with 165 msec continuous AP activity spanning the 125 msec isoelectric interval between P waves. Pacing the AP produced identical P waves. We conclude: Sustained reentry can occur within AP networks mimicking atrial flutter and fibrillation, and may account for the unusually high incidence of these arrhythmias in WPW pts.

INTRAOPERATIVE USE OF SOCK AND PLAQUE ELECTRODES IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME.

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Intraoperative mapping with a hand-held probe electrode requires a sustained rhythm lasting 5-10 minutes. To overcome this limitation, we studied 16 WPW patients using a computerized system that maps from 60 electrodes simultaneously. A sock, with 6 rows of electrodes from base to apex, is placed over the ventricles. The time from placing the sock to analyzing the base row of electrodes is 5 minutes. A plaque with 2.5mm interelectrode spacing is then placed over the early site at the AV groove for detailed mapping. During plaque recording, the rest of the sock recordings are analyzed and a complete epicardial map is drawn in an additional 8 minutes. This technique rapidly detects early activation at the AV groove as do other computer systems using only a band of electrodes at the AV groove. The addition of complete epicardial mapping is important, because in 2 patients with septal pathways, the site of ventricular breakthrough was below the strip recorded by the AV band. Complete epicardial maps allowed us to study rapidly changing or short-lived electrical events including isolated premature impulses, initiation and termination of reciprocating tachycardia (RT) by pacing, entrainment and changing degrees of fusion by pacing during RT, and the ventricular response during the onset, maintenance and termination of atrial fibrillation. This technique offers specific advantages over the hand-held probe or computer systems with only an AV band of electrodes.

EFFECTS OF ELECTRODE CATHETER SHOCKS DELIVERED NEAR THE TRICUSPID ANNULUS IN DOGS

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In order to assess the feasibility of using electrical discharges to interrupt right free wall accessory pathways, a series of shocks (S) were delivered from a percutaneously inserted electrode catheter positioned fluoroscopically at a number of sites around the tricuspid annulus (TA) to a chest wall patch (anode) in dogs. S were 50J (6 sites), 100J (2), 200J (5) or 400J (3). Endocardial electrograms (atrial(A) and ventricular (V)), right ventriculograms and pressures were recorded before and after S. Transient atroventricular block and unsustained ventricular tachycardia were frequent; 1 dog had ventricular fibrillation but none died. Ten days later, no evidence of tricuspid regurgitation or right heart decompensation was found. On gross examination, evidence of transmural damage was found with S of greater than 200J but there were no perforations. Endocardial lesion area correlated with energy delivered, from 62 mm^2 for 50J to 221 mm^2 for 400J. When the ratio of the A to V electrogram amplitude was 1.0 to 1.5, the lesion extended to the TA ; when less than 1.0, the center of the lesion was below the TA. Mild coronary artery adventitial inflammation was seen at 2 sites (200J and 400J) and medial inflammation in 1 (400J). We conclude that this catheter technique yields reproducible damage of the atrial wall adjacent to the TA in such a distribution that it may prove suitable for interrupting right free wall accessory pathways in humans.

Monday, March 10, 1986
10:30AM–12:00NOON, Room #364/365
The Mitral Valve: Structural Features in Health and Disease

PHENOTYPIC HETEROGENEITY IN MITRAL VALVE PROLAPSE: RELATION OF MITRAL VALVE ABNORMALITIES TO BODY WEIGHT AND BLOOD PRESSURE

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To relate anatomic and functional mitral valve (MV) abnormalities to other phenotypic features of MV prolapse (MVP) we analyzed computerized 2-dimensional echo MV images frame-by-frame through 1 cardiac cycle in 30 patients (pts) with MVP and 23 age & sex matched controls. Posterior mitral leaflet length (PML), mitral anular diameter and the % change in anular diameter from early to late systole (%Δanulus) were measured, and time-motion echoes reconstructed to detect motion of points equally spaced along the leaflets versus intracardiac reference frames. 14/30 MVP pts exhibited systolic MV billowing into the left atrium (type 1 MVP) and 16 did not (type 2 MVP). Time-motion reconstruction showed typical M-mode MVP independent of overall heart motion in 8/16 pts with type 2 MVP on the single cycle analyzed. Measurements in MVP pts and controls:

	Controls	MVP-1	MVP-2
PML (cm/M^2)	0.81±0.11	0.97±0.17**	0.88±0.19
Anulus (cm/M^2)	1.52±0.23	1.68±0.24*	1.60±0.36
%ΔAnulus	19±13	22±12	38±13***
Weight/height (cm/kg)	0.41±0.08	0.40±0.05	0.34±0.03**
Systolic BP (mm Hg)	129±20	126±18	116±13*

Significance vs controls: *p<0.05, **p<0.005, ***p<0.001

Thus, quantitative 2-D echo reveals 2 patterns of MVP, both associated with typical M-mode and auscultatory features, type 1 with fixed mitral leaflet and anular enlargement and leaflet billowing, type 2 with dynamic systolic expansion of the mitral anulus in pts with a phenotype with low body weight and blood pressure.

IN VIVO VALIDATION OF A NONPLANAR MITRAL ANNULAR SHAPE: IMPLICATIONS FOR THE DIAGNOSIS OF MITRAL VALVE PROLAPSE

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By cross-sectional echocardiography (2DE), the mitral leaflets (MLs) appear to be displaced above the mitral annulus (MA) in the apical four-chamber (A4C) view in a surprisingly high percent of normals, but bear a normal relation to the MA in orthogonal views. This discrepancy can be explained in 2 ways: 1) the MA is planar and true leaflet displacement occurs in only 1 view; or 2) the MA is nonplanar, as suggested by animal studies, and lies on a hyperbolic paraboloid. The second theory predicts that the MLs will lie below the apparent MA plane in views intersecting the most superior points of the MA, and above it in views through the lowest points. To address this question we studied 16 patients (pts) age 13-79 selected for apical image quality. Excluded were pts with calcified MA, LV dysfunction, and rheumatic or infective mitral disease. Serial LV apical 2DE views were obtained at 30° rotational intervals. The MA was defined as the ML hinge points and its 3-dimensional systolic configuration was reconstructed based on the rotational geometry. RESULTS: Vertical distance of MA points from the transducer along the rotational axis was plotted against angle of rotation. In all 16 pts, this curve was bimodal with maxima near the aorta and posterior LV wall and minima medially and laterally. The difference between the most apical and basal points was .6-1.9cm (mean 1.3). CONCLUSION: The MA is nonplanar in the pts studied, lying along a hyperbolic paraboloid. The apparent discrepancy in ML-MA relation in apical views can be attributed to MA configuration without actual ML displacement above the most superior MA points. These findings challenge the assumption of a planar MA and the diagnosis of prolapse in many otherwise normal people.

FLOPPY MITRAL VALVES: ABNORMAL MECHANICAL PROPERTIES-BASIS FOR ELONGATION AND RUPTURE OF CHORDAE TENDINEAE.

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Abnormal elongation and rupture of chordae tendineae (CT) are common findings in patients with severely floppy mitral valves (FMV). To understand the mechanism of these chordal abnormalities, we tested the hypothesis that CT from FMV have different mechanical properties than CT from normal mitral valves (NMV). Fifteen CT from 5 FMV (surgery) and 20 CT from 6 NMV (autopsy) were tested in an uniaxial tension mode in an Instron machine. Load vs elongation curves were obtained for each CT until fracture. CT of similar diameter were used in both FMV and NMV to determine fracture stress and fracture strain. Fracture stress (fracture load/original cross-sectional area) and fracture strain (total elongation/original CT length) were calculated for each CT. Data are shown (mean ± 1SD).

	Fracture Stress (10^8 dynes/cm^2)		Fracture Strain (%)
FMV Total (n=15)	2.96±1.96	p<0.01	27.3±6.5
NMV Total (n=20)	5.62±1.60		27.6±11.9
FMV Free Margin (n=8)	1.83±0.51	p<0.01	26.9±4.3
NMV Free Margin (n=9)	5.13±1.26		24.6±10.9

CT from FMV had lower mean fracture stress than CT from NMV. CT attached to the free margins of the FMV leaflets had the lowest fracture stress when compared to any other CT ($p<0.05$). Fracture strain in CT from FMV was not statistically different compared to CT from NMV. Thus, the grossly abnormal fracture stress may be contributing to the rupture of CT in patients with FMV.

SURGICAL PATHOLOGY OF THE MITRAL VALVE: STUDY OF 628 CASES.

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To determine whether the causes of mitral disease have changed appreciably in the past 2 decades, we reviewed grossly the mitral valves from 628 patients who had undergone mitral valve replacement at our institution during 1965, 1970, 1975, or 1980. Postinflammatory (including rheumatic) disease accounted for 78% of 628 cases and for 99% of 416 with mitral stenosis with (263) or without (151) regurgitation; 2 valves were congenitally stenotic. Among 212 patients with clinically pure mitral regurgitation, floppy valves accounted for 37%, postinflammatory 34%, ischemic disease 10%, infective endocarditis 7%, cardiomyopathy 3%, chordal rupture 3%, congenital anomaly 2%, and chronic aortic regurgitation 1%; the cause was indeterminate in 2%. The relative incidence of clinically pure mitral regurgitation due to a floppy valve increased during each of the 4 years of the study, accounting for 17% of 29 cases in 1965 and 57% of 49 cases requiring mitral valve replacement in 1980. In postinflammatory cases, there were more females (71%) but with floppy valves there were more males (73%). At our institution, postinflammatory disease was the most common cause for excision of mitral valves in each of the 4 years of the study; its relative incidence has not changed appreciably since 1965. Our findings suggest that (i) the incidence of chronic rheumatic disease has not yet begun to diminish or (ii) many episodes of acute rheumatic fever may be subclinical or (iii) some forms of nonrheumatic mitral valve disease may produce gross alterations indistinguishable from chronic rheumatic valvulitis.

PEPTIDERGIC INNERVATION IN HUMAN MITRAL VALVE: ALTERATIONS IN MITRAL STENOSIS AND PROLAPSE.

Jose M. Brum, M.D., Lester E. Wold, M.D., William D. Edwards, M.D., Vay L. W. Go, M.D., Alfred A. Bove, M.D., Ph.D., F.A.C.C., Mayo Clinic, Rochester, MN.

The human mitral valve has been considered to be devoid of sensory innervation. If present, a sensory function of the mitral valve could contribute to local regulation of myocardial function. Recently nerve structures have been described in human heart valves. Substance P (SP), a neuro peptide related with sensory nerve activity, is present in human heart nerves. To determine if SP exists in human mitral valves, cadaver valves (n=6) were collected in a period of 4 to 16 hours postmortem (PM). Pathoanatomic examination excluded cardiac diseases. Mitral valve samples (n=11) were also collected from patients referred for valve replacement surgery for mitral stenosis (MS), mitral valve prolapse (MVP), and papillary muscle rupture (PR). Radioimmunoassay technique determined concentration (ng/g) of SP-like immunoreactivity (SP-LI). SP-LI was present in all samples (0.27±0.08) of the PM group. In the MS group 4 of 8 valves showed SP-LI (0.56±0.11). MVP patients had no SP-LI in the valves. The highest SP-LI was found in a patient with PR (1.40 ng/g). The presence of SP-LI in PM normal valves contrasts with the absence of SP-LI in 4 of 8 MS and MVP patients. The results suggest that alteration of mitral valve peptidergic sensory innervation occurs in mitral valve disease.

FUNCTIONAL PATHOLOGY OF MITRAL REGURGITATION IN ACTIVE RHEUMATIC CARDITIS - SURGICAL AND ECHOCARDIOGRAPHIC OBSERVATIONS.

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Active rheumatic carditis (ARC) was confirmed at operation in 61 black pts subjected to correction of severe mitral regurgitation (MR). Mitral valve replacement was performed in 34 pts and mitral valvuloplasty in 27. Histological corroboration of the diagnosis was available in 48 pts. In 13 pts, all of whom underwent valvuloplasty, insufficient tissue was submitted for histological assessment. Sixteen pts also required aortic valve replacement. There were 40 females and 21 males with a mean age of 13± 4 (SD) yrs. All pts presented in NYHA Class III (36 pts) or Class IV. Mean cardiothoracic ratio was 66±7 (SD) %. Severity of MR was confirmed by the following intraoperative pressures (mmHg): mean LA=26±9 (SD) with a V wave = 49±18 (SD); LV end diastolic = 16±6 (SD). Preoperative 2-D and M-mode echo demonstrated marked prolapse of the anterior mitral leaflet (AML) in 57 pts. At operation AML prolapse was confirmed in all 57. Of these 57, mitral anular dilatation was found in 54 (95%), chordal elongation in 50 (88%) and chordal rupture in 4 (17%). Of the total 61 pts, some fibrosis and retraction of mitral leaflet tissue was noted in 8. We conclude that AML prolpase is the most consistent valvular abnormality in severe MR caused by active rheumatic valvulitis. It results from chordal elongation which is almost invariably accompanied by anular dilatation. Chordal rupture was rare in this study.

Monday, March 10, 1986
10:30AM–12:00NOON, Room #157
Cardiac Transplantation

DEVELOPMENT OF CORONARY ATHEROSCLEROSIS IN THE TRANSPLANTED HEART IMMUNOSUPPRESSED WITH CYCLOSPORINE AND PREDNISONE

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Coronary atherosclerosis (CA) is a late sequelae post-cardiac transplantation (TX) in patients (pts) treated with azathioprine and prednisone (pred) but the prevalence of CA and associated factors have not been evaluated in pts post-TX on cyclosporine (Cy) and pred immunosuppression. In this group of pts we found by coronary arteriography CA in 19% (11/57 pts) at 1 year; 17% (4/24 pts) at 2 years, and 45% (5/11 pts) at 3 years. Of the 8 pts studied more than once, 6 (75%) developed CA after the first year. Recurrent (2 or more) major rejection episodes diagnosed by endomyocardial biopsy were associated with a higher prevalence of CA (47% vs 9.5% without recurrent rejection, $p<0.05$ at 1 year, 43% vs 6% at 2 years $p<0.05$). Use of antiplatelet agents [aspirin (A) and persantine (P)] was associated with a lower prevalence of CA (11.5% CA on A/P vs 26% CA not on A/P at 1 year; 12.5% CA on A/P vs 25% CA without A/P at 2 years) but these trends did not reach statistical significance. A pre-TX history of CA was not a predisposing factor for post-TX CA. Of 6 pts who died within 1 year after coronary arteriography, 5 had no CA by coronary arteriography but had CA at autopsy.

These data demonstrate that CA develops in post-TX pts treated with Cy and pred and is probably underestimated by coronary arteriography. CA appears to be related to recurrent rejection and may be ameliorated by antiplatelet agents.

HYPERLIPIDEMIA AND HYPERTENSION FOLLOWING HEART TRANSPLANTATION: POTENTIAL CAUSES OF CORONARY ATHEROSCLEROSIS? Diane M. Becker, Sc.D., Maria Markakis, B.S., Michael Sension,B.S., Susan Vitalis, B.S., Kenneth Baughman, M.D., F.A.C.C., Thomas A. Pearson, M.D, Ph.D. Johns Hopkins Medical Institutions, Baltimore, MD.

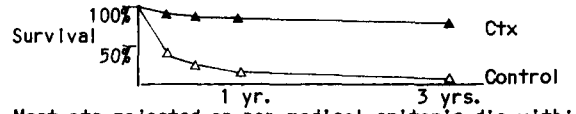
Coronary atherosclerosis remains a significant cause of heart transplant (HtTr) failure, yet factors responsible for this have been poorly documented. To study the potential contribution of known coronary risk factors, we examined blood pressure, serum lipids, exercise, smoking and diet in 27 patients from 3 to 24 months following HtTr. Post transplant, no patients smoked, 67% had a regular aerobic exercise regimen, and 70% followed a low salt, prudent diet. Although only one patient had hypertension prior to HtTr and all patients were on antihypertensive pharmacotherapy post transplant, 84% had blood pressure 140/90 by 3 months post HtTr. Most striking was a progressive rise in mean total serum cholesterol from a pre HtTr level of 171 mg.% +/- 36 mg.% to mean levels of 239 mg.%, 263 mg.%, and 302 mg.% at 3, 6, 9 months respectively post HtTr, with no further rise of levels thereafter. Cholesterol levels pre HtTr and 3 months post HtTr did not correlate well with later levels, while 6 month levels predicted levels at 9, 12, 18, and 24 months post HtTr ($p=.01$). In patients 6 months post HtTr, triglyceride levels (x=156 mg.% +/- 94 mg.%) and HDL cholesterol levels (x=52 mg.% +/- 16 mg.%), were within normal limits but LDL cholesterol (x=142 mg.% +/- 46 mg.%) and apoprotein B levels (x=121 mg.% +/- 38 mg.%) were markedly elevated. LDL cholesterol level correlated with time since HtTr ($p=.02$) but not with predisone dose, diet or exercise. Screening of blood pressure and serum lipids 6 months post HtTr will identify a high prevalence of hypertension and Type II hyperlipoproteinemia, which may be amenable to treatment. Identification and reduction of these two known risk factors may be beneficial in reducing the risk of late coronary atherosclerosis in HtTr.

PATIENTS DENIED CARDIAC TRANSPLANTATION FOR NON-MEDICAL CRITERIA: A CONTROL GROUP. L. Warner Stevenson, M.D., Michael B. Fowler, M.D., John S. Schroeder, M.D., F.A.C.C., Kathleen A. Dracup, R.N., Suzanne H. Clark, R.N., Victoria Fond. UCLA and Stanford Medical Centers, Los Angeles and Stanford, California.

Cardiac transplantation (Ctx) has not been tested against present medical therapy in a controlled trial. To determine the benefit of Ctx we defined as a control group 36 patients (pts) evaluated since 1981 who were found medically eligible but were denied Ctx on other criteria. For 32 pts, hemodynamics and outcomes could be obtained and compared to those of pts undergoing Ctx.

Criteria for rejection were psychological status in 15 pts, financial status in 8, patient indecision in 5, and body size in 4. Control pts were actually less compromised than pts receiving Ctx, but there were no significant differences in clinical class (control 3.4 vs. 3.8 Ctx), cardiac index (1.9 vs. 1.7 L/min/m^2), pulmonary wedge pressure (26 vs. 27 mmHg), or right atrial pressure (12 vs. 12 mmHg).

Four pts underwent Ctx elsewhere. For the remaining 28 control pts, 24 of whom received vasodilators, actuarial survival at 3 mos. was 40% compared to 88% after Ctx, at 6 mos. 21% vs. 86%, 1 yr. 13% vs. 84%, and at 3 yrs. 7% vs. 72%. *2 of 3 control pts surviving 3 yrs. had* initially decided against transplantation. 14/25 deaths in the control group were sudden, the remainder related to hemodynamic deterioration.



Most pts rejected on non-medical criteria die within 3 mos. although occasional long-term survival does occur. Ctx offers significant improvement in survival when compared to current medical therapy.

THE DEVELOPMENT OF TRICUSPID REGURGITATION AFTER ORTHOTOPIC CARDIAC TRANSPLANT

Marc K. Lewen DO, Robert J. Bryg MD, Leslie W. Miller MD, George A. Williams MD FACC, Arthur J. Labovitz MD FACC, St. Louis University School of Medicine, St. Louis, MO

In order to assess the incidence and etiology of tricuspid regurgitation (TR) after orthotopic cardiac transplantation, the files of 18 surviving transplant patients (range 1-37 months, mean 14.5 months) were reviewed. Patients ranged in age from 10-56 years with 8 having idiopathic congestive cardiomyopathy, 7 ischemic cardiomyopathy, 2 valvular heart disease and 1 congenital heart disease. Serial echocardiography and Doppler evaluation of all valves, hemodynamics, grade of rejection, and the cold storage time of the transplanted heart were analyzed. TR was demonstrated by Doppler in 16/18 patients, 9 with moderate to severe (mod/sev) TR and 7 with mild TR. Of the 9 patients with mod/sev TR, 4 had PA systolic pressure of 60 mmHg or greater prior to transplantation while only 1 patient with mild TR had a preop PA systolic pressure of 60 mmHg. Of the patients with mod/sev TR, 8/9 had right ventricular volume overload (RVVO) pattern by echocardiography while only 2/7 with mild TR had RVVO. Two patients with significant TR had torn tricuspid chordae. TR developed within the first month after transplantation in most patients. There was no relationship between the development or severity of TR with age, cold storage time, grade of rejection or post transplant hemodynamics. Although 16/18 had TR, no patients required treatment for right heart failure after one month. In conclusion: 1) TR occurs in most patients after orthotopic cardiac transplantation. 2) Severe pulmonary hypertension prior to transplantation predisposed the recipient to the development of mod/sev TR. 3) Despite the echocardiographic findings of RVVO, TR is well tolerated post transplantation.

SYSTOLIC AND DIASTOLIC VENTRICULAR FUNCTION AT REST AND DURING EXERCISE IN HEART-TRANSPLANT PATIENTS.

Mario S. Verani, M.D., F.A.C.C., James B. Young, M.D., F.A.C.C., Avanindra Jain, M.D., Sameh Tadros, M.D., H. David Short, M.D., George P. Noon, M.D., F.A.C.C., Robert Roberts, M.D., F.A.C.C., Michael E. DeBakey, M.D., F.A.C.C. The Methodist Hospital, Baylor College of Medicine, Houston, TX.

Little is known about the functional adaptations of the transplanted heart. Accordingly, we assessed the systolic and diastolic ventricular performance after cardiac transplantation (T) in 13 patients, aged 17-56 (median 42 years), using radionuclide angiography before, early post-T (median 4 days) and late post-T (median 114 days). All patients had myocardial biopsy just prior to the studies. Supine bicycle exercise was performed in 10 patients undergoing late studies. In all early and late post-T studies, the right atrium appeared dilated and akinetic although all patients were in sinus rhythm. The LV ejection fraction (EF) improved from 19 ± 10% (mean ± SD) pre-T to 61 ± 6% early post-T ($p < .001$). The LV peak diastolic filling rate (PDFR) was normal (3.6 ± 1.0 EDV/sec) early post-T. These variables remained normal at the late study. The RV-EF was also normal in the early (44 ± 4%) and late studies (47 ± 7%). Patients exercised for 420 ± 149 seconds and increased the LV-EF from 56 ± 4 to 62 ± 10% ($p < .05$) and RV-EF from 47 to 54% ($p < .03$). Eight of 10 patients increased the LV-EF normally (by ≥ 5%). Similarly, exercise PDFR increased, from 2.9 ± .4 to 3.6 ± 1.0 EDV/sec (ns). The only patient with a fall in exercise LV-EF had class 2 rejection by biopsy. The other patients had either normal biopsy (n = 5) or minimal rejection (n = 3). Thus, despite abnormal atrial function, rest and exercise systolic and diastolic ventricular function are usually preserved late after cardiac transplantation.

ELECTRICAL PULSE TRAINS TO ACTIVATE LATISSIMUS DORSI MUSCLE CHRONICALLY FOR POTENTIAL CARDIAC AUGMENTATION

John D. Mannion, M.D., Michael A. Acker, M.D., Aida S. Khalafalla, Ph.D., Stanley Salmons, Ph.D., Larry W. Stephenson, M.D., F.A.C.C., Hospital of the University of Pennsylvania, Philadelphia

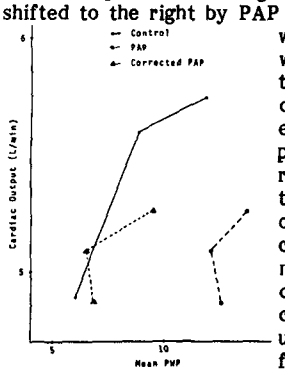
Patients with hypoplastic or failing ventricles could be helped by auxiliary ventricles (AV) constructed from fatigue-resistant skeletal muscle. We have already made canine latissimus dorsi muscle (LDM) more fatigue resistant by continuous low-frequency electrical stimulation for 6 weeks. Recently we constructed AVs from electrically conditioned LDMs. They were connected to the circulation and generated significant pressure and flow for 4 hours. Unconditioned AVs fatigued (< 4 mins). The chronic effects on the LDM of electrical pulse trains of the type needed to accuate an AV are, however, unknown. The LDMs of 3 groups of 3 dogs each were therefore stimulated with a 45 Hz burst pattern (100 ms on; 400 ms off) or continuous patterns at 2 and 10 Hz. At the end of 6 wks all 9 stimulated LDMs had acquired a uniformly Type I fatigue-resistant histochemical profile which was found in only 45 ± 7.6% of contralateral control muscles. Histologic architecture was preserved. In stimulated LDMs the content of slow myosin increased and fast decreased. All stimulated muscles fatigued significantly more slowly than controls ($P < 0.05$). Thus, burst patterns suitable for chronic actuation of AVs are not only well tolerated by the LDMs but are as effective as 2 and 10 Hz conditioning frequencies in producing improved fatigue resistance.

Monday, March 10, 1986
10:30AM–12:00NOON, Room #267
Considerations in Measuring Cardiac Function

A METHOD OF ESTIMATING LEFT VENTRICULAR PRELOAD IN THE PRESENCE OF POSITIVE AIRWAY PRESSURE IN MAN.

Roy V. Ditchey, M.D., FACC, JoAnn Lindenfeld, M.D., FACC, Jose Pacheco, M.D., FACC, and Karen Dawson, RN, University of Colorado Health Sciences Center, Denver, CO

Positive airway pressure (PAP) causes similar increments in intrapericardial and intracavitary right ventricular end-diastolic pressures in dogs. For this reason, and because right ventricular pressure constitutes part of the effective "external" pressure acting on the left ventricle via the interventricular septum, subtraction of the effects of PAP on right heart filling pressures accurately corrects left ventricular filling pressures for the effects of PAP on intrathoracic pressure in this model. To determine whether these concepts can be applied clinically, we measured cardiac output (CO) and pulmonary wedge and central venous pressures with and without 15 cmH20 of continuous PAP under 3 filling conditions in 5 patients. The relationship between wedge pressure and cardiac output was shifted to the right by PAP in each case (i.e., wedge pressure was higher for any CO). However, when wedge pressures measured in the presence of PAP were corrected by subtracting the effects of PAP on central venous pressure, the wedge-CO relationship was shifted back toward control in each case, with overlap of mean control and corrected wedge pressures at matched cardiac outputs. We conclude that the increment in central venous pressure can be used to correct wedge pressures for the effects of PAP in man.



VARIABILITY OF RIGHT HEART OXYGEN SATURATIONS IN ADULTS WITH AND WITHOUT LEFT-TO-RIGHT INTRACARDIAC SHUNTING.

L. David Hillis, MD, FACC, Brian G. Firth, MD, D Phil, FACC, and Michael D. Winniford, MD, U of Texas Health Science Center, Dallas, TX.

The oximetric detection of intracardiac left-to-right shunting requires knowledge of the variability of oxygen measurements in the right heart chambers of patients without shunting. Previous studies have examined this variability in a relatively small number of subjects without shunting and have based their limits of acceptability on multiple measurements of oxygen content or saturation in each right heart chamber. It is the practice in many catheterization laboratories and intensive care units to measure the oxygen saturation of single blood specimens from the superior vena cava (SVC), right atrium (RA), and pulmonary artery (PA) during right heart catheterization, but no previous study has assessed the variability of such single measurements in adults with and without intracardiac left-to-right shunting. We measured the oxygen saturations of SVC, RA, and PA single blood samples in 961 adults [492 men, 469 women, aged 50 ± 13 (mean ± SD) years]. In the 912 without intracardiac shunting, the differences in oxygen saturation between SVC and RA, RA and PA, and SVC and PA were 3.3 ± 2.6%, 2.1 ± 1.9%, and 3.5 ± 2.7%, respectively, so that the normal limits of variability (mean ± 2SDs) for these oxygen saturation differences were 8.5%, 5.9%, and 8.9%, respectively. Of the 49 patients with intracardiac shunting, these limits of variability correctly identified 44 (90%), and the 5 with shunting whose saturation differences were below these limits had small shunts (Qp/Qs ratios ≤ 1.9). Thus, an assessment of oxygen saturations from single blood specimens from SVC, RA, and PA offers excellent sensitivity, specificity, and predictive accuracy in identifying patients with and without shunting.

INFLUENCE OF PRELOAD AND AFTERLOAD ON POST-EXTRASYSTOLIC POTENTIATION IN NORMAL SUBJECTS AND PATIENTS WITH VALVULAR HEART DISEASE

Thomas Wisenbaugh, M.D., Anthony DeMaria, M.D., Veterans Administration and University of Kentucky Medical Centers, Lexington, KY

The role of altered preload and afterload in post-extrasystolic potentiation(PESP) of LV performance is uncertain. Simultaneous cineangiography and micromanometry were therefore performed for control and PESP beats in 20 pts: 10 normals(NL) and 10 with severe valvular disease (VHD): 4 with aortic regurgitation, 3 with aortic stenosis, 3 with mitral regurgitation. Measures of LV performance were: ejection fraction(EF), end systolic(ES) volume index (VI,cc/M^2), and mean normalized systolic ejection rate (MNSER,sec^{-1}). LV pre- and afterload were measured as end diastolic (ED) VI and mean systolic stress (MSS,kdyn/cm^2), respectively: (mean ± STD, *p .05 vs C)

	NL		VHD	
	Control	PESP	Control	PESP
EF	0.66±0.04	0.75±0.05*	0.59±0.09	0.70±0.09*
MNSER	2.33±0.73	2.89±0.99*	1.77±0.36	2.33±0.51*
ESVI	24±7	19±7	58±34	45±29*
EDVI	69±19	74±19*	137±56	141±55
MSS	153±54	140±49	175±44	170±40

A smaller increase in EDVI with PESP in VHD (3%) than NL (8%) was associated with a reduced index of LV compliance (dV/VdP at ED=.020 mmHg-1 vs .062 for NL, p 0.01). Thus, although utilization of preload reserve contributed to PESP in NL, favorable changes in length and load did not account for substantial PESP of ventricular performance with hemodynamic overload imposed by VHD. These data indicate that augmented inotropic state is the major determinant of PESP in man.

A PULSED DOPPLER ECHOCARDIOGRAPHIC STUDY OF TRANSMITRAL FLOW IN PATIENTS WITH DILATED CARDIOMYOPATHY

Katsu Takenaka, MD, Ali Dabestani, MD, Julius M Gardin, MD, FACC, Alice Allfie, Sandra Clark, Walter L Henry, MD, FACC. University of California, Irvine, California.

Doppler echocardiography has proven useful in evaluating LV diastolic function by assessing early diastolic filling. Although patients with dilated cardiomyopathy (DCM) are known to have abnormal LV diastolic compliance and relaxation, early diastolic LV filling has been reported to be normal. To further evaluate this apparent discrepancy, we measured peak flow velocity (PFV) in early and late diastole (in cm/sec), ratio of late-to-early diastolic PFV, and deceleration time of early filling flow (in msec) from Doppler mitral flow recordings in 21 DCM patients with mitral regurgitation (MR), 6 DCM patients without MR and 19 age-matched normal subjects. Results (mean) were as follows:

	Diastolic PFV Early	Late	Late Early	Early Flow Decel. Time
Normals	53.0	47.1	0.95	174
DCM with MR	61.4	37.0	0.63	112*
DCM without MR	34.2*	48.7	1.83*	103*

*p < 0.05 compared to normal values

Early diastolic PFV, late diastolic PFV and the ratio of late-to-early diastolic PFV were not significantly different in DCM patients with MR from values in normal subjects. In contrast, DCM patients without MR had evidence of abnormal LV filling as indicated by a lower early diastolic PFV and a higher ratio of late-to-early diastolic PFV than normal. The deceleration time of early filling flow was shorter than normal in both groups. Thus, with the exception of an abnormally rapid deceleration of early filling flow, mitral regurgitation appears to mask LV filling abnormalities in patients with dilated cardiomyopathy.

PREDICTORS OF POSTOPERATIVE LEFT VENTRICULAR DYSFUNCTION FOLLOWING OPERATION FOR CHRONIC MITRAL REGURGITATION.

G.J. Kontos, Jr., M.D., A.A. Bove, M.D., F.A.C.C., H.V. Schaff, M.D., F.A.C.C., N.H. Lazarow, M.D., and B.J. Gersh, M.B., Ch.B., D.Phil., F.A.C.C., Mayo Clinic, Rochester, MN 55905.

To determine whether preoperative indices of LV performance predict postoperative low CO, we studied 17 patients undergoing valve replacement or repair for chronic mitral regurgitation. Preoperative systolic LV performance was quantitated with pressure volume analysis from ventriculograms, and patients were divided into Group I, 9 patients with no postoperative low CO, and Group II, 8 patients with postoperative low CO requiring inotropic support. Ten patients without overt heart disease were controls.

	EJF	EDVI	LVMI	M/V	ESWS/ESVI
I	61±8	142±72†	140±65†	1.04±0.43	3.8±2.3
II	63±11	111±19†	90±25*	0.82±0.22†	3.4±1.2†
Control	67±8	63±14	68±17	1.11±0.32	5.5±2.5

Abbreviations: EJF=ejection fraction; EVDI=end-diastolic volume index (ml/m^2); LVMI=left ventricular mass index (gm/m^2); M/V=ratio of LVMI to EDVI; ESWS/ESVI=ratio of end-systolic wall stress to end-systolic volume index.

*p<0.05 vs I; †p<0.05 vs control

Results indicate that patients with low CO following correction of mitral regurgitation have inadequate compensatory LV hypertrophy. Neither extent of LV dilatation nor indices of LV systolic function identified patients with postoperative low CO, but indices of LV mass and M/V ratio may be useful predictors.

NONINVASIVE MEASUREMENT OF PEAK AORTIC BLOOD ACCELERATION WITH CONTINUOUS WAVE DOPPLER FOR THE ASSESSMENT OF LEFT VENTRICULAR PERFORMANCE IN PATIENTS.

Hani N. Sabbah, B.S., Fareed Khaja, M.D., F.A.C.C., James F. Brymer, M.D., F.A.C.C., Thomas M. McFarland, M.D., David E. Albert, M.D., and Paul D. Stein, M.D., F.A.C.C.
Henry Ford Hospital, Detroit, Michigan

Peak aortic blood acceleration (peak dV/dt) has been recognised as a sensitive index of global left ventricular performance. In the present study peak dV/dt was assessed noninvasively in patients using a continuous wave Doppler velocity meter (ExerDop®). Peak instantaneous aortic velocity (V) and peak dV/dt were measured by placing the ultrasonic transducer at the suprasternal notch. Measurements were made in 36 patients undergoing diagnostic cardiac catheterization. Peak V and peak dV/dt were measured just prior to left ventriculography. At least 14 consecutive sinus beats were averaged in each patient. Left ventricular ejection fraction (EF), calculated from ventriculograms obtained in the right anterior oblique projection, ranged from 20 to 87%. Peak dV/dt, measured noninvasively, showed a good linear correlation with EF, (r = 0.90) and a somewhat better power fit, r = 0.93. Peak V had a less close linear correlation with EF (r = 0.77). These results indicate that peak dV/dt, measured with continuous wave Doppler, relates closely to EF and, therefore, can be used as a noninvasive indicator of global LV performance.

Monday, March 10, 1986
10:30AM–12:00NOON, Room 268
Young Investigators' Awards Competition

The following six abstracts were from the winning entries in the Young Investigators' Awards Competition, 35th Annual Scientific Session.

THE VASOCONSTRICTIVE RESPONSE FOLLOWING ARTERIAL ANGIOPLASTY IN PIGS: EVIDENCE FOR VASOCONSTRICTION RESULTING FROM RATHER THAN CAUSING PLATELET-DEPOSITION.

J.Y.T. Lam, M.D., J.H. Chesebro, M.D., F.A.C.C.
L. Badimon, Ph.D., and V. Fuster, M.D., F.A.C.C., Mayo Clinic, Rochester, MN 55905.

Whether vasoconstriction (VC) causes or results from platelet deposition (PD) on the arterial wall is unclear. Agents such as Prostacyclin (PGI_2) and Thromboxane A_2 (TxA_2) or their antagonists which affect platelet function and vascular tone in vitro may assist in defining the in vivo relationship between VC and PD. We examined this relationship in normal pigs that were sacrificed immediately after angioplasty of the carotid arteries (5 inflations to 6 ATM, 30 seconds each, 1 minute apart): 24 control pigs and 17 pigs treated with intravenous PGI_2 50 (50 ng/kg/min, n=8), or SQ 29,548, a selective TxA_2 antagonist (0.1 mg/kg bolus then 5 µg/kg/min, n=9). PD was quantitated using the ^{111}In-labeled PD of the dilated segment (x 10^6/cm^2). The degree of VC (average % diameter narrowing proximal and distal to the dilated segment) was measured from angiographic films taken before and after angioplasty. PGI_2 50 and SQ 29,548 decreased VC to 18 ± 3% (p<.04) and to 15 ± 3% (p<.03) respectively vs control (31 ± 3%), without affecting PD (52.6 ± 17.3 and 21.3 ± 4.3 respectively vs 34.5 ± 9.2 for control, P=NS). VC was directly related to PD in controls (r=0.77, p<.001), and PGI_2 proportionately decreased VC for any given PD, whereas SQ 29,548 decreased VC independent of PD. Since VC correlated directly with PD in controls and since TxA_2 receptor blockade and PGI_2 infusion decrease VC without decreasing PD, VC appears to be the result rather than the cause of PD. PGI_2/TxA_2 balance appear more important for vasomotor tone control, rather than the regulation of PD in vivo, when the thrombogenic stimulus from severe arterial wall injury is great.

FATTY ACID ACCUMULATION IS A MARKER OF MYOCYTE VIABILITY IN ISCHEMIC-REPERFUSED MYOCARDIUM

D. Douglas Miller, M.D., John B. Gill, M.D., Martha Barlai-Kovach, B.A., Mark A. Nedelman, B.A., H. Thomas Aretz, M.D., David R. Elmaleh, Ph.D., Charles A. Boucher, M.D., F.A.C.C., H. William Strauss, M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA

To examine the relationship of fatty acid uptake (FAU) to viability in ischemic-reperfused myocardium, 10 dogs had a 15 min (n=5) or 60 min (n=5) left anterior descending coronary occlusion with a 3 hr reperfusion. Microsphere myocardial blood flow (MBF) was measured during occlusion (Sr) and after release (Sc). I-125 FA analog was given (100uCi I.V.) with Sc at 3 hr of reperfusion. Paired ultrasonic crystals assessed regional left ventricular (LV) systolic shortening (%SS). Myocyte ultrastructure was determined by electron microscopy (EM) of 3 hr reperfusion biopsies as normal (++), reversibly (+) or irreversibly (-) injured. Ischemic LV segments (MBF <0.5ml/min/gm) were classified as staining triphenyltetrazolium chloride positive [T.T.C.(+); n=169] or T.T.C. (-) [n=37] for comparison of FAU, MBF, 3 hr %SS and EM to normal segments (] = p<0.05):

LV SEG	MBF-Sr	FAU	FAU/MBF-Sc	3hr%SS	EM
Normal	.80±.3	.24±.06	.35±.09]	35± 6]	++
TTC(+)	.24±.2	.26±.04]	.38±.10]	8±22]	+
TTC(-)	.20±.2	.19±.09]	.30±.16]	1± 7]	-

Ischemic regions became dyskinetic during occlusion (%SS = -11±4). Infarcted [T.T.C.(-)/EM(-)] segments remained akinetic, while viable [T.T.C.(+)/EM(+)] zones recovered partial systolic function at 3 hr of reperfusion. Segmental FAU and FAU/MBF-Sc were significantly increased (by 37 and 27%, respectively) in T.T.C.(+) ischemic segments over that in infarcted segments. FAU/MBF-Sc was also 9% greater than normal in viable ischemic myocardium. A 60 min occlusion-3 hr reperfusion model adapted for in vivo single photon emission computed tomography (SPECT) showed a similar excess of I-123 FA analog activity over flow (thallium-201) in the ischemic border zone of 4/4 canine myocardial infarcts.
We conclude that FA analog accumulation noninvasively identifies ischemically stunned but viable myocardium that may be salvaged by sustained reperfusion.

PHOTOSENSITIZATION OF EXPERIMENTAL ATHEROMAS BY PORPHYRINS

Marc E. Pollock, M.D., John Eugene, M.D., F.A.C.C., Marie Hammer-Wilson, M.S. and Michael W. Berns, Ph.D., VAMC, Long Beach and University of CA, Irvine.

Arteriosclerotic arteries have been shown to fluoresce when treated with Hematoporphyrin Derivative (HPD). If porphyrins are localized in the atheromatous plaque, these plaques should be sensitized to appropriate wavelength laser radiation. We studied the incorporation, distribution and photosensitizing properties of a partially purified form of HPD (Photofrin II) in normal and arteriosclerotic rabbit aortas. A thoracoabdominal exploration was performed in 15 rabbits. Group I contained normal rabbits, Group II contained normal rabbits given 5 mg/kg Photofrin II pre-op, Group III contained arteriosclerotic rabbits and Group IV contained arteriosclerotic rabbits given 5 mg/kg Photofrin II 48 hours pre-op. Multiple aortic biopsies for frozen section were taken from all rabbits. In addition, open laser endarterectomy (with an argon ion laser) was performed on Group III and Group IV rabbits. Frozen sections were studied by Digital Video Fluorescence Microscopy to determine the distribution of Photofrin II within the layers of the aortic wall. The fluorescence of the intima of Group IV rabbits was found to be significantly (p<.01) higher than the fluorescence of the intima, internal elastic lamina, media or adventitia of the other groups as well as significantly (p<.01) greater than the fluorescence of the internal elastic lamina, media or adventitia of Group IV rabbits. When open laser endarterectomy was performed, Group III rabbits required 103±14 J/cm^2 and Group IV rabbits required 33±3 J/cm^2 (p<.01). We conclude that porphyrins are selectively localized within the intima of arteriosclerotic arteries. This localization sensitizes atheromas to argon ion laser light and facilitates laser endarterectomy.

EFFECTS OF RYANODINE AND CAFFEINE ON CONTRACTILITY, MEMBRANE VOLTAGE AND CA EXCHANGE IN CULTURED CHICK EMBRYO VENTRICULAR CELLS.

Carl A.F. Rasmussen, Jr., M.D., PhD., John L. Sutko, PhD. and William H. Barry, M.D., F.A.C.C., Brigham and Women's Hospital Boston, MA.

To investigate the mechanisms of action of ryanodine and caffeine, and the role of the sarcoplasmic reticulum (SR) in excitation-contraction (E-C) coupling; we correlated changes in mechanical and electrical activity caused by these agents with alterations in ^{45}Ca fluxes and cell Ca contents in chick embryo ventricular cell monolayer cultures. Ryanodine (10^{-10} to 10^{-5}M) irreversibly decreased contraction amplitude by 10 to 70% in a concentration dependent manner with minimal effects on electrical activity. Ryanodine (10^{-6}M) caused a decrease in rapid ^{45}Ca uptake, no change in total exchangeable Ca content and no change in rapid ^{45}Ca efflux relative to control measurements. These results suggest that ryanodine decreases the release of Ca^{2+} from the SR without depleting the SR of Ca^{2+}. Caffeine (1 to 20mM) caused a transient (less than 10sec) increase in contraction amplitude (5 to 12% greater than control), followed by a sustained (maximal after more than 15sec) decrease in contraction amplitude (9 to 76% less than control) and a decrease in diastolic membrane voltage (10 mV). Caffeine caused a decrease in rapid ^{45}Ca uptake, a decrease in total exchangeable Ca content and an increase in rapid ^{45}Ca efflux. These results suggest that caffeine produces a decrease in SR Ca^{2+} uptake, and/or an increase in SR Ca^{2+} release that eventually depletes the SR of Ca^{2+} to account for its biphasic inotropic effects. Our data in cultured chick embryo ventricular cells support an important role for the SR in E-C coupling, and indicate that SR Ca^{2+} is part of the rapidly exchanging Ca^{2+} compartment noted in ^{45}Ca flux studies.

DIFFERENTIAL CONTROL OF HEART RATE AND SYMPATHETIC NERVE ACTIVITY DURING DYNAMIC EXERCISE IN HUMANS. Ronald G. Victor, M.D. CV Center & VA Med Center, University of Iowa, Iowa City, IA.

This study tested the concept that central command (CC) and muscle chemoreflexes (MCR) trigger mass sympathetic discharge at the onset of dynamic exercise in humans. In 19 healthy subjects, I measured heart rate (HR) and muscle sympathetic nerve activity (MSNA) with microelectrodes in the peroneal nerve during 2 min of rhythmic handgrip (RHG) at 10-50% max with and without arrested forearm circulation. During nonischemic RHG, MSNA did not increase even at 50% max but HR rose by +11±5 bpm (x±SE, $p<0.05$). In contrast, during forearm ischemia RHG at only 30% max increased MSNA by 77±15% ($p<0.05$). This suggests that, during small muscle exercise, CC increases HR but MCR must be engaged to trigger increases in MSNA. To study exercise of larger muscles, I measured responses during 2-arm cycling (2 min bouts) at 0-60 watts (W) in 6 subjects. During cycling at 0-20W, HR rose rapidly (ΔHR=+22±3 bpm at 20W, $p<0.05$) but MSNA did not change. However, during heavier exercise, MSNA increased ($p<0.05$) by 69±16% at 40W and by 121±24% at 60W. Even at these high work loads, MSNA rose only after the first 30 sec of exercise when HR had already increased by >25 bpm. Thus, although HR increases promptly at the onset of even mild large muscle exercise, activation of MSNA occurs more slowly and at a much higher threshold workload.

In conclusion, these findings challenge the concept of mass sympathetic discharge at the onset of exercise and indicate striking differences in the control of HR and MSNA during rhythmic contraction of both small and large muscle groups. I suggest that these differences relate to highly differential effects of CC and MCR on heart rate and muscle sympathetic outflow.

Monday, March 10, 1986
2:00PM–3:30PM, Room #313/314
Pediatric Doppler Echocardiography

EVALUATION OF FETAL CARDIAC HEMODYNAMICS BY COLOR DOPPLER Dev Maulik, M.D., Navin C. Nanda, M.D., F.A.C.C., Ming C. Hsiung, M.D., James P. Youngblood, M.D., University of Alabama, Birmingham, Alabama

Color Doppler (CD) studies were performed in 17 pregnant subjects. CD allowed ready identification of fetal heart through detection of dynamic flow patterns. Visual recognition of flow patterns which filled the whole of vessel lumen facilitated not only alignment of Doppler cursor parallel to flow but also reproducible measurement of internal diameters of PA (imaged in aortic short axis view) and ascending aorta (imaged in apical 5 chamber view) for reliable estimations of RV and LV stroke volumes (SV, ml) in 8/17 (48%) fetuses.

Fetal age (weeks)	22	25	32	34	34	36	38	39
RVSV (ml)	0.4	1.5	3.1	2.1	4.8	3.6	3.9	3.9
LVSV (ml)	0.2	0.8	1.7	1.1	2.5	1.7	2.1	1.9
Ratio	2.0	1.9	1.8	1.9	1.9	2.0	1.8	2.0

Inferior vena caval flow, always turbulent (mosaic color), was seen to split into two components-70% directed into RA and RV, 30% along eustachian valve through foramen ovale and its valve into LA. Superior vena cava flow was laminar. Considerable flow was also seen entering descending aorta from PA through ductus arteriosus. CD permits, for the first time, real time composite characterization of fetal intracardiac flow patterns and should thus be superior to conventional Doppler in assessing normal and abnormal hemodynamics.

BENEFICIAL EFFECTS OF SUPEROXIDE DISMUTASE OR ALLOPURINOL AFTER CANINE MYOCARDIAL ISCHEMIA AND REPERFUSION. S. Werns, M.D., M. Shea, M.D., K. Gallagher, Ph.D., S. Phan, Ph.D., M.D., B. Pitt, M.D., F.A.C.C., and B. Lucchesi, Ph.D., M.D., The University of Michigan Medical School, Ann Arbor,Michigan 48109

Reperfusion injury of ischemic myocardium may be due to oxygen radicals generated by xanthine oxidase or neutrophils. Therefore, in an occlusion-reperfusion model of myocardial ischemia, we evaluated treatment with: superoxide dismutase (SOD) (5 mg/kg over 2 hours starting 15 minutes pre-occlusion via the left atrium) or allopurinol (A) (25 mg/kg 18 hours pre-occlusion and 50 mg/kg 15 minutes pre-occlusion via peripheral vein). Anesthetized dogs (12-17 kg) underwent a left circumflex coronary artery occlusion for 90 minutes. Animals were sacrificed after either 6 h of reperfusion to measure infarct size (n=10) or 6 weeks of reperfusion to measure scar thickness and collagen concentration (n=15). Infarct size as a percentage of the area at risk was: controls 41±3 †, A 20±6 ††, and SOD 18±2 ††. The differences are not due to differences in rate-pressure product, an index of myocardial oxygen demand. Neither drug improved collateral blood flow as measured with radioactive microspheres. The ratios of scar to normal LV thickness were: controls .89±.03 and SOD .91±.03 ($p > .05$). The scar collagen concentrations were: controls 2.9±.5 and SOD 3.5±.4 ($p > .05$). Thus, both SOD and A salvaged myocardial tissue, and SOD did not alter scar thickness or collagen concentration. Therefore, scavengers of oxygen radicals may prevent reperfusion injury of ischemic myocardium without deleterious effects on infarct healing.

† All data expressed as $\bar{x} \pm$ SEM
†† $p < 0.05$ vs control

PULSED DOPPLER DIAGNOSIS OF ATRIOVENTRICULAR VALVE INSUFFICIENCY IN UTERO James C. Huhta, MD, FACC, Daniel J. Murphy, MD, Robert J. Carpenter, MD. Sections of Cardiology and OB/GYN, Dept. of Pediatrics, Baylor College of Medicine/Texas Children's Hosp., Houston, Texas.

Atrioventricular valve insufficiency (AVVI) has been suggested as a sign of fetal distress in utero. Pulsed 2D-directed Doppler echocardiography was utilized for the detection of AVVI in 50 fetuses ranging in gestational age from 16-39 weeks. AVVI was diagnosed when a systolic velocity >1 meter per second was detected in either atrium and had the typical holosystolic appearance which identified it as AVVI and not ventricular outlet velocity. AVVI was present in 8/50 (16%) fetuses and confirmed after birth in 5/5. Of 30 fetuses at risk for congenital heart disease but found to have normal anatomy, 1 had AVVI (3%). Of 11 fetuses with dysrhythmia, 3/3 with complete heart block (1 normal and 2 with atrioventricular canal) had intermittent AVVI, while 7 with premature atrial contractions and 2 with atrial tachycardia had none. Of 9 fetuses with abnormal cardiac findings, 5 had AVVI (cardiomyopathy-1, cerebral arteriovenous malformation-1, Ebstein's with pulmonary atresia-1, and Rh disease-2). Two patients with a normal heart and hydrops had no AVVI.

Conclusions: (1) AVVI occurs in utero and may be diagnosed by pulsed Doppler echocardiography. (2) AVVI may be present in normals, with fetal dysrhythmia, or with congenital or acquired cardiac dysfunction. It is not present in all forms of nonimmune hydrops fetalis and cannot be interpreted as a specific sign of fetal distress.

REAL-TIME DOPPLER COLOR FLOW MAPPING FOR ASSESSMENT OF PATCH AND BAFFLE LEAKS AFTER SURGERY FOR CONGENITAL HEART DEFECTS. Kyung J. Chung, M.D., F.A.C.C., Frederick S. Sherman, M.D., David J. Sahn, M.D., F.A.C.C., Sandra Hagen-Ansert, R.D.M.S., Richard E. Swensson, M.D., F.A.C.C., Lilliam M. Valdes-Cruz, M.D., F.A.C.C., Univ of Calif, San Diego, CA.

Two-dimensional color flow mapping was performed on 18 patients (PTS) beginning 36 hours after closure of ventricular septal defects (VSD) or intraatrial baffling procedures for transposition of the great arteries (TGA). Six PTS had simple VSD, 5 were studied after tetralogy of Fallot repair, 2 after repair of atrioventricular septal defect and 5 after a Senning or Mustard procedure. Of 7 VSD patch leaks detected, 4 were posteriorly and superiorly located and adjacent to tricuspid valve tissue under the septal leaflet. Three posterior leaks disappeared by the second postoperative week and were not detectable by Doppler flow mapping or by auscultation at a 4 - 6 month followup examination. The last one remains detectable by Doppler and by auscultation. Two PTS had VSD patch leaks at the superior, anterior edge, adjacent to the aortic valve and one had a residual leak adjacent to the pulmonary valve after closure of a supracristal VSD. In these latter 3 PTS, the shunt remained detectable beyond 6 months and it has been surgically verified in 2. Of the 5 TGA PTS, 3 had baffle leaks localized at the superior rightward edge of the baffle at the superior vena caval-right atrial junction. Left-to-right shunts detected in this area persisted for 1 yr and were confirmed by catheterization in 2 PTS 1 yr. postop. We conclude that color flow mapping is extremely sensitive for localizing patch and baffle leaks after surgery for congenital heart disease and that the position of a leak may have prognostic significance.

POST OPERATIVE OBSTRUCTION OF PULMONARY VENOUS RETURN: DETECTION WITH PULSED DOPPLER ECHOCARDIOGRAPHY.
J. Geoffrey Stevenson, M.D., F.A.C.C., James W. French, M.D., F.A.C.C., Isamu Kawabori, M.D., Stanley J. Stamm, M.D., Dale G. Hall, M.D., Edward A. Rittenhouse, M.D., Peter B. Mansfield, M.D. Children's Orthopedic Hospital and University of Washington, Seattle, Wa.

The diagnosis of post operative pulmonary venous obstruction (ObPVR) after repair of anomalous pulmonary venous return (TAPVR) or transposition (TGA) can be difficult clinically but early detection is important for effective care of these patients.

To evaluate whether Doppler echocardiography is useful in detection of ObPVR, we measured peak blood flow velocities (maxV) at the anastomotic site of TAPVR repair in 4 patients, and throughout the pulmonary venous atrium in 12 patients with Mustard repair of TGA. Exams were done 1 month to 10 years post-op. In the TAPVR group, 2 were obstructed (wedge $\bar{m}$=23&25mmHg), and had high maxV(2.2&3.6 M/sec). Two without obstruction had significantly lower wedge pressures ($\bar{m}$=15&12mmHg), and maxV(1.1&1.2M/sec). With TGA, 5 were obstructed (wedge 24-37, $\bar{m}$=29.8mmHg),and had pulmonary venous atrial velocities which were significantly higher (maxV 2-2.8, $\bar{m}$2.3M/sec) than those in the 7 without obstruction (maxV 0.9-1.3, $\bar{m}$1.1M/sec). Distinctive features of Doppler flow in obstruction were high peak velocity (about twice normal), and turbulence, either in diastole or throughout the cardiac cycle. Timing of flow depended upon post-obstructive atrial capacity. With obstruction near the AV valve, small post-obstruction chamber, flow was largely limited to diastole. Doppler echocardiography appears sensitive and very useful in detection of post operative ObPVR.

OBSTRUCTION TO PULMONARY VENOUS RETURN IN CHILDREN WITH CONGENITAL HEART DISEASE—DETECTION BY DOPPLER
G. Wesley Vick, III, MD, PhD, Achi Ludomirsky, MD, W. Robert Morrow, MD, James C. Huhta, MD, FACC, Daniel J. Murphy MD, Mary J. H. Morriss, MD, FACC. Section of Cardiology, Dept. of Pediatrics, Baylor College of Medicine/Texas Children's Hospital, Houston, Texas.

Obstruction to pulmonary venous return (OPVR) occurs in a number of congenital cardiovascular abnormalities and hemodynamic assessment by cardiac catheterization (cath) may be difficult. A noninvasive method for detection and quantitation of OPVR would be useful clinically. Using 2D directed pulsed and continuous wave Doppler we examined, prior to cath, 28 patients thought clinically to have possible OPVR. Primary diagnoses included transposition of the great arteries status post venous baffle repair-9, total anomalous PVR-8 (2 post surgical repair), cor triatriatum-7 (4 post surgical repair), and congenital mitral stenosis-4 (1 post surgical repair). Severe OPVR was predicted if Doppler examination measured a diastolic flow velocity >2 m/sec at any level of the left atrial or left ventricular inflow.

At cath 9/28 patients had severe OPVR (gradient $\geq$16 mmHg) and all were correctly detected by Doppler (no false negatives). The site of pulmonary venous obstruction was localized accurately by 2D/Doppler in all. Mild OPVR correlated with a biphasic or continuous flow velocity pattern with peak velocities <2 m/s.

Conclusions: (1) 2D/Doppler accurately detects severe pulmonary venous obstruction in children with congenital heart disease. (2) This technique should be useful in the selection of patients for cath—particularly when pulmonary venous obstruction is suspected postoperatively.

DETECTION OF CORONARY FLOW BY PULSED DOPPLER AND COLOR DOPPLER FLOW MAPPING AND ITS DIFFERENTIATION FROM PULMONARY INSUFFICIENCY. Franco Recusani, M.D., Lilliam M. Valdes-Cruz, M.D., F.A.C.C., Nancy Dalton, R.D.M.S., David J. Sahn, M.D., F.A.C.C., Brian Hoit, M.D.. Univ of Calif, San Diego, CA.

Pulmonary insuffiency(PI) by Doppler has been reported in as many as 90% of normal subjects. We interrogated the RV outflow tract (RVOT) area with color flow Doppler (CD) (Aloka 880) and pulsed wave Doppler (PD) (Irex Exemplar) in 3 open chest dogs, in 24 normal volunteers, in 13 patients (PTS) with proven PI and in 25 PTS without PI undergoing left and right heart catheterization. In the dogs, diastolic flow towards the transducer (TX) in the RVOT area was seen by CD and the timing and duration of flow was confirmed by spectral and MQ displays. Saline injections (INJ) through an AO root catheter enhanced the signal while PA INJ's did not enhance either the systolic or diastolic signals. In the normals, diastolic flow in the RVOT area was detected by CD and PD in 22/24; it was holo or end diastolic lasting 60-170msec into systole after the onset of the QRS; maximal velocity = 95-150 cm/sec. In the 13 PTS with proven PI, the RVOT diastolic flow was shorter, earlier, and differed in time-velocity sequence from the flow detected in controls. In the catheterized PTS without PI, RVOT area diastolic flow identical to controls was detected by PD in 20/25 and AO root echo-contrast INJ enhanced the diastolic signals for 2-3 cardiac cycles in all. PA INJ did not augment the signals. We conclude that the majority of normal persons have diastolic flow signals in the RVOT area which probably represent flow from one of the branches of a coronary artery sampled as an error of azimuthal (planar) resolution. This flow must be distinguished from PI and sometimes from a patent ductus arteriosus, especially in patients evaluated for surgery without catheterization.

Monday, March 10, 1986
4:00PM–5:30PM, Room #313/314
Stress Echocardiography

PREDICTION OF THE PRESENCE AND LOCATION OF CORONARY ARTERY DISEASE BY DIGITAL EXERCISE ECHOCARDIOGRAPHY

Charles G. Vasey, M.D., William F. Armstrong, M.D., F.A.C.C., Thomas Ryan, M.D., Paul L. McHenry, M.D., F.A.C.C., Harvey Feigenbaum, M.D., F.A.C.C.; Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis, Indiana

Cineangiograms and digital exercise echocardiograms (EE) were compared in 88 patients (pts) with presumed coronary artery disease (CAD) to define the ability of EE wall motion abnormalities (WMA) to predict the presence and location of specific coronary artery lesions. Supine two-dimensional echocardiograms were performed in parasternal and apical views immediately before and after treadmill exercise and were digitized in a continuous loop, quad screen format. Comparable rest and exercise views were displayed side by side. CAD was defined as a $\geq$ 50% diameter narrowing. Anterior WMA (anterior wall, apex or anterior septum) were present either at rest or with exercise in 45 pts, 42 of whom had left anterior descending or diagonal CAD. Posterior WMA (inferior, posterior or lateral walls) were present in 48 pts, 45 of whom had circumflex or right CAD. Left anterior descending CAD was present in 16 of 17 pts with exercise-induced anterior WMA. Circumflex or right CAD was present in all 15 pts with new posterior WMA.

	Sensitivity	Specificity	Accuracy	Predictive Value
Any Anterior WMA	84	92	88	93
Any Posterior WMA	87	92	89	94
New Anterior WMA	67	97	83	94
New Posterior WMA	68	100	87	100

False-negative EE occurred most frequently in pts whose exercise heart rates were less than 100. EE were considered technically difficult but interpretable in 7 pts. We conclude that digital EE can accurately predict the presence and location of CAD.

DOPPLER AORTIC FLOW VELOCITIES DURING EXERCISE; RELATION TO EVIDENCE OF MYOCARDIAL ISCHEMIA BY THALLIUM PERFUSION SCINTIGRAPHY

Michael R. Harrison, MD, Mikel D. Smith, MD, Bruce J. Friedman, MD, FACC, Oi Ling Kwan, Anthony N. DeMaria, MD, FACC, University of Kentucky and VAMC, Lexington, KY

Doppler(DOP) detection of abnormal blood flow velocity produced by exercise-induced myocardial ischemia(ISC) might provide a simple non-invasive technique to assess the presence or prognosis of coronary artery disease. However, few data are available regarding changes in blood flow velocity(VEL) measured by DOP during exercise induced ISC. Thus, we measured VEL in the ascending aorta by continuous wave DOP positioned in suprasternal notch in 6 controls (CON) and 40 patients(pts) undergoing exercise thallium scintigraphy (TH). Studies were performed in the standing position prior to and immediately after maximal treadmill exercise. TH was interpreted in the standard fashion and was normal in 17 pts, revealed only infarction (INF) in 6, and manifested a reversible defect indicative of ISC in 17. Coronary angiography was concordant with TH in 24 of 25 pts in whom it was performed. DOP measurements were obtained from the outer border of the spectral record, and included peak VEL and flow VEL integral(FVI) from onset to termination of flow. Results: (mean, p=non-significant for all)

	CON	NL	INF	ISC
Peak VEL (% increase)	59.5	57.1	40.2	38.8
FVI (% increase)	48.0	33.9	35.4	27.5

Flow VEL measurements varied widely in each group. Although VEL showed the greatest increase during exercise in control and normal, 11 of 17 pts with ISC showed comparable increase. Peak VEL post-exercise was decreased in 2/17 pts with ISC by TH, and 1/17 normals. FVI after exercise was reduced in 3/17 pts with ISC and 4/17 normals. Thus, although the increase in VEL by DOP with exercise is slightly less in pts with INF or ISC, variability of response limits the application of this method in individual pts. The response of aortic flow VEL to exercise does not enable the identification of myocardial ischemia.

SUPRASTERNAL EXERCISE DOPPLER (EXERDOP): FEASIBILITY AND RESULTS IN NORMALS AND PATIENTS WITH SUSPECTED CORONARY DISEASE.

Thomas A. Kelly MD, Robert M. Rothbart MD, Vincent J. Patrone MD, Jane C. Moore MEd, Denny D. Watson PhD, Robert S. Gibson MD. Univ. of VA, Charlottesville, VA

Animal studies with Doppler have shown that blood flow velocity(V) and acceleration(A) rise progressively during simulated exercise. With induced ischemia, these values decrease. To evaluate the clinical utility of Exerdop(E) in humans, 76 normals(NL) had E during graded treadmill exercise (GXT). E was performed at rest, 2 min into each Bruce stage and immediately post-GXT. Group (G) I included 35 NLs (20-40 yrs) and GII comprised 41 NLs (40-70 yrs). Technically adequate E studies were obtained in all 76 subjects through 4 stages of Bruce GXT and proved highly reproducible based on 3GXTs with E in 30 GI subjects.

20-40 years (n=35)			40-70 years (n=41)		
	A (dV/dt)	Velocity		A (dV/dt)	Velocity
Rest	25.9± 7.0	0.74±.12	Rest	15.3± 4.77	0.60±.17
1	33.3±12.8	1.17±.23	1	30.7±10.57	1.00±.20
2	41.0±15.5	1.33±.28	2	42.3±14.67	1.14±.22
3	50.5±20.3	1.44±.26	3	50.1±14.36	1.27±.26
4	58.7±23.0	1.54±.27	4	54.4±17.45	1.27±.26
Post	64.2±19.1	1.48±.30	Post	61.5±16.34	1.52±.29

Compared to GI, GII had lower rest V and A values ($p=0.0001$) and lower V at all GTX stages($p\leq.01$). E was performed on 11 additional pts who underwent exercise Tl-201 for suspected CAD. All 8 pts with normal Tl-201 had a progressive ↑ in exercise V, despite 5 false positive ECGs; 3 pts with exercise-ischemia by Tl-201 had ↓ exercise V ($p=.012$). Thus: 1)E is a technically feasible adjunct to routine GXT; 2)older NL individuals have lower rest A and V values, and reduced V during exercise; and 3)decreased V during exercise appears to distinguish true vs false positive GXT.

DIPYRIDAMOLE-TWO DIMENSIONAL ECHOCARDIOGRAPHY: A TEST FOR DETECTING TRANSIENT ISCHEMIC CHANGES IN LEFT VENTRICULAR WALL MOTION

Alberto Margonato MD, Sergio Chierchia MD, Gillian Smith BSc, Graham Davies MRCP, Filippo Crea MD, Attilio Maseri MD FACC, Rodney Foale MD. Cardiovascular Unit, RPMS, Hammersmith & St Mary's Hospitals, London, UK.

Exercise echocardiography has recognized limitations due to movement artifacts. To overcome this problem we used two dimensional echocardiography (2DE) during dipyridamole (D) administration as a means for detecting transient ischemic regional wall motion abnormalities (RWMA) in angina pectoris. 23 patients with effort angina and positive exercise tests, who had technically satisfactory 2DE were studied. All had angiographically significant coronary artery disease, 8 with 3 and 15 with 2 vessels involved. 2DE was recorded in parasternal short axis views of the left ventricle during control, D infusion (0.6 mg/kg i.v. over 4 minutes) and recovery. Regional wall motion was compared during infusion to control and recovery by two blinded observers in consensus. D induced RWMA in 11 patients (D positive) after 163 ± 92 seconds (range 66 – 330 seconds). ECG changes and pain (9 patients) always occurred later (301.2 ± 98.9 and 358.2 ± 88.9 seconds after D respectively). The localization of RWMA was well correlated with the angiographic severity of coronary lesions. In 10 patients (D negative), no RWMA, ECG changes or pain were observed during D. In 2 patients the results were considered equivocal due to extensive dyskinesia in the control 2DE. In D positive, angina at rest was more common (10 patients vs 5 patients P=0.055) and coronary disease more severe than in D negative. Furthermore, D positive showed a lower coronary reserve during exercise than D negative (time to 1mm ST depression 172 ± 170 and 472 ± 179 seconds respectively, $p<0.05$). In conclusion : 1) D-2DE is an effective alternative to exercise 2DE for the detection of RWMA in patients with severe coronary disease. 2) The test may have value in precise geographic localisation of ECG changes and may allow the identification of the ischemia-related vessel in patients with 2 or 3 vessel disease.

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DIPYRIDAMOLE-ECHOCARDIOGRAPHY TEST IN PATIENTS WITH EXERCISE - INDUCED ST SEGMENT ELEVATION.

Eugenio Picano MD, Michele Masini MD, Alessandro Distante MD, Fabio Lattanzi MD, Antonio L'Abbate MD FACC. C.N.R., Clinical Physiology Institute, University of Pisa, ITALY.

Aim of this study was to test the hypothesis that dipyridamole (DIP) could offer a clue to the assessment of the underlying coronary anatomy (and, possibly, of the pathogenetic mechanism) in patients (pts) with effort induced ST elevation. Seventeen consecutive pts with exercise induced ST segment elevation, in the absence of previous infarction and basal left ventricular asynergy, performed DIP- test (i.v. DIP, 0.56 mg/Kg in 4 min. during 12 lead ECG and 2-D echocardiographic monitoring). In 9 pts, DIP induced ST segment elevation, in the same leads which showed ST elevation on effort. A reversible asynergy (occurring in the region corresponding to the ECG leads with diagnostic changes) could always be documented by echocardiography. In 2 pts, DIP induced a reversible asynergy in the presence of ST depression. In all these 11 pts, angiography invariably showed a severe (>90%) organic stenosis in the coronary artery feeding the transiently impaired region after DIP; 7 pts had single, 4 had double vessel disease. In the remaining 6 pts (all of whom with either spontaneous or ergonovine induced ST elevation), DIP did not induce either ST elevation or depression or regional asynergy, coronary angiography showed absent (3 pts) or significant (3 pts) coronary artery disease. It is concluded that DIP may induce transmural ischemia, as detected by the electrical hallmark of ST elevation, reproducing effort - induced ST elevation. In these cases, a severe organic stenosis is always present in the coronary artery feeding the transiently asynergic myocardial region.

DOPPLER MONITORED HEMODYNAMIC RESPONSE AND EARLY ISCHEMIA IN EXERCISE STRESS TESTING PREDICTS TRIPLE VESSEL DISEASE.

Nawzer Mehta, B.Sc., David Bennett, F.R.C.P., Keith Dawkins, M.D., David Ward, F.A.C.C., and David Mannering, B.Sc., St. George's Hospital Medical School, London, England.

A positive ECG exercise stress test with a poor hemodynamic response has been associated with a high 1 year mortality in post-infarction patients. We have monitored non-invasively, the hemodynamic response to exercise in 31 patients with a positive exercise stress test (Bruce protocol) 3 weeks post-infarction, by measuring the maximum acceleration of ascending aortic blood using Doppler ultrasound. Maximum acceleration was obtained at rest and peak exercise, and expressed as a percentage change (% ΔMA). The time to onset of ST segment depression (STons) (>1mm depression 80 msecs after J-point) was also noted. All patients subsequently had coronary angiography and were categorized into those with >70% stenosis in 1, 2 or 3 coronary vessels. The results are presented as mean values ±SEM. Statistical significances are related to 3 vessel disease.

Vessels Diseased	N	%ΔMA	p	STons	p
1	16	28.7 ±6.7	≤0.01	5.3 ±0.5	≤0.001
2	9	32.1 ±8.5	≤0.01	3.1 ±0.5	≤0.01
3	27	12.3 ±2.0		1.8 ±0.2	

A poor Doppler response was defined as a <25.3% increase in maximum acceleration (the mean +1SD of the value for 3 vessel disease patients); similarly a poor STons was defined as <3 minutes. Using these criteria the sensitivities and specificities of these variables in identifying 3 vessel disease were ascertained.

	%ΔMA	STons	Combined
Sensitivity	89%	93%	89%
Specificity	60%	60%	76%

Thus, a combination of an attenuated Doppler monitored hemodynamic response and early ischemia during exercise is highly predictive of triple vessel disease. The Doppler technique may thus be a useful adjunct to routine exercise stress testing in identifying high mortality risk patients in the setting of myocardial infarction.

Monday, March 10, 1986
2:00PM–3:30PM, Room #264/265/266
Thrombolysis I

THROMBOLYTIC TREATMENT OF ACUTE MYOCARDIAL INFARCTION WITH RECOMBINANT – TISSUE TYPE PLASMINOGEN ACTIVATOR: CORONARY STATE AFTER 4 WEEKS

W.G. Schmidt M.D., R. v. Essen M.D., R. Uebis M.D., S. Effert M.D., W. Rutsch M.D. *, M. Schartl M.D. *, H. Schmutzler M.D. *, R. Erbel M.D. **, J. Meyer M.D. (on behalf of the European Cooperative Study Group for Recombinant Tissue–Type Plasminogen Activator rt–PA).**

Dept. of Int. Medicine I, RWTH, Aachen; Dept. of Cardiology, Klinikum Charlottenburg, Free University, Berlin **; Dept. of Int. Medicine II, University of Mainz **.

91 patients (pts.) with acute myocardial infarction (AMI) of less than 6 h of duration were randomly assigned to treatment with intravenous Streptokinase (SK) or rt–PA as part of the randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous SK in AMI. 45 pts were allocated to rt–PA treatment (group P), 46 pts (group S) received SK. After treatment the infarct related coronary vessel was patent in 37/45 pts. (82 %) of group P and 27/46 pts. (59 %) of group S. In 7 cases of unsuccessful thrombolysis the vessel could be recanalized mechanically. PTCA of the residual stenosis was performed in 17 cases. After successful reperfusion, all pts. received 25.000 U of heparin per day up to the control examination.

3 – 4 weeks later, a second angiogram could be obtained in 48 pts. 3/48 vessels were reoccluded (2/29 in group P and 1/19 in group S). Reocclusion occured in 1/14 cases with an initial residual coronary stenosis of ≥ 90 % of diameter, and in 2/28 cases with 50–90 %. In only 6 pts. (12.5 %), the residual obstruction was less than 50 %, all having patent arteries in the control angio.

In 33 cases without PTCA the degree of coronary artery narrowing could be assessed quantitatively both immediately after reperfusion and 3–4 weeks later on; there was a decrease from 74 ± 14 % to 56 ± 17 % of diameter ($p < 0.05$; group P: 74 ± 17 to 56 ± 21 %, n = 16, group S: 74 ± 9 to 57 ± 12 %, n = 17). However, in 27/33 pts. (82 %) the residual stenosis remained to be ≥ 50 %.

Thus, a patent infarct related artery is seen more often after treatment with rt–PA as compared to SK. The incidence of reocclusion and the regression of stenosis are similar in group S and P. Despite a significant decrease the residual stenosis usually remains to be more than 50 % of diameter within a follow-up period of 4 weeks. This should be considered concerning further treatment of pts. with special regard to PTCA and bypass surgery.

EFFECT OF INTRAVENOUS THROMBOLYTIC THERAPY ON LV FUNCTION - REPORT FROM THE NHLBI THROMBOLYSIS IN MYOCARDIAL INFARCTION(TIMI) TRIAL

Florence H. Sheehan, M.D., for the TIMI Investigators, NHLBI, Bethesda, M.D.

TIMI Phase I randomized 290 patients(pts) <7h after acute myocardial infarction(MI) to recombinant tissue plasminogen activator(rTPA) or streptokinase(SK). Change (△) in EF and hypokinesis in the MI region(HYPO) measured by the centerline method were determined in 153 patients(pts) who had analyzable pre-treatment (pre-tr) and pre-discharge (pre-dc) contrast ventriculograms. Although pts with reperfusion(R) were more likely to have pre-dc cath, improvement in EF was insignificant in both treatment groups (paired t for △ pre-tr to pre-dc: *p<.001, #p<.05)

rTPA: △EF=0.8±7.0 (N=82), △HYPO=0.4±0.8,(N=75)*
SK: △EF=1.4±8.1 (N=71), △HYPO=0.4±0.8,(N=65)*

In combined SK and rTPA pts with known R status, HYPO and EF improved in pts with total occlusion (occ) and R (Group A). HYPO improved in pts with subtotal occ (Group B). Neither improved in pts with permanent occ (Group C), late R occurring between caths (Group D), or rethrombosis (Group E):

Group/N	A/49	B/25	C/29	D/29	E/10
△EF	2.5±6.9#	2.9±8.8	-1.0±6.6	0.7±8.6	0.5±7.5
△HYPO	0.4±0.7*	0.8±0.9*	0.1±0.7	0.3±0.8	0.0±0.5

In Group A, EF improved in pts with R <4h after MI (△EF=4.3±7.2# (N=22) vs 1.0±6.3 (N=27,p=NS for R later than 4h).

Thus thrombolytic therapy with SK and TPA results in significant improvement in regional wall motion in the infarct site. However significant improvement in EF was seen only in patients who achieved sustained reperfusion. The increase in EF was greatest in the subset who were reperfused within 4 hrs after MI.

HAZARDS OF USING POST THROMBOLYTIC ST SEGMENT EVOLUTION AS A REPERFUSION MARKER. OBSERVATIONS FROM THE TIMI TRIAL

George B. Bren, MD; Alan G. Wasserman, MD, FACC; Allan M. Ross, MD, FACC; for the TIMI Investigators, Washington, DC

Decisions regarding secondary strategies to preserve reperfused artery patency after IV lytic therapy for MI would be served by a reliable marker of lysis. As the use of ST segment elevation (ST↑) evolution for this purpose has been controversial we interrogated ECG data on 273 MI pts in the NHLBI Phase I Thrombolysis in Myocardial Infarction Trial (TIMI). Infarct lead ST↑ was centrally digitized on admission (Adm) and 2 hours after IV Streptokinase or rTPA (2hp̄). Time from pain onset to treatment was 4.8h. We compared groups with initially completely obstructed arteries with subsequent substantial reperfusion (REPER), no reperfusion (NOREP) and those with initially incomplete obstruction (INCOMP).

	REPER	NOREP	INCOMP
Adm ST↑	.38mV±.22	.38mV±.27	.32mV±.17
2hp̄ST↑	.13mV±.11←p<.002→	.19mV±.18 ←p<.0001→	.09mV±.10

Although there is less ST↑ at 2hp̄ in REPERF vs NOREP patients, the absolute difference is only .06 mV. Similar findings were seen when pts were stratified by infarct location and with analysis restricted to those treated ≤4 hours. We also evaluated sensitivity (SENS) and specificity (SPEC) of ST↑ magnitude at 2hp̄ and magnitude of decline in ST↑ (ΔST) from adm to 2hp̄ for identifying vessel patency post treatment.

	ST↑≥.2mV at 2h	ST↑≥.1mV at 2h	ΔST≥.2mV	ΔST≥.3mV
SENS	78%	55%	55%	33%
SPEC	40%	64%	58%	76%

Conclusion: ST segment evolution is not clinically reliable for distinguishing reperfused from non-reperfused patients.

HEPARIN INDUCES CORONARY REPERFUSION IN VERY EARLY MYOCARDIAL INFARCTION.

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Heparin is not a thrombolytic drug, but interferes with components of the coagulation cascade to inhibit fibrin generation. If given early, it might prevent maturation of an obstructive intracoronary platelet aggregate to a stable fibrin thrombus. On this rationale, we gave a 7500-10000 unit bolus of intravenous Heparin (IVH) to 15 hospitalized patients who were seen during the first one hour of acute myocardial infarction (MI). All had ongoing ischemic chest pain and new ST segment elevations ≥ 2 mm in at least 2 contiguous leads, unresponsive to sublingual or intravenous nitrates or both. Relief of pain and abrupt return of ST segments to (10) or toward (1) baseline occurred within 20 minutes in 11 patients (73%). Of these, none developed new pathologic Q waves. Two had no creatine phosphokinase (CPK) elevations greater than 150% of laboratory normal and 9 had early peaking CPK curves consistent with coronary reperfusion. Eight of these 11 had coronary angiography within 72 hours after IVH showing patency of the infarct-related vessel in all. No bleeding complications occurred in patients receiving IVH alone. Thus IVH appears to induce reperfusion when administered during the first 1 hour of acute MI and may be a safe, effective substitute for thrombolytic drugs in that situation.

THE TIME INTERVAL FROM INITIATION OF IV STREPTOKINASE TO REPERFUSION IS DIRECTLY RELATED TO THE RESIDUAL FIBRINOGEN LEVEL AND IS SHORTENED BY PRETREATMENT WITH HEPARIN.

Allan S. Lew MD, Bojan Cercek MD, Pierre Laramee MD, Hanoch Hod MD, P.K. Shah MD, FACC and William Ganz MD, CSc, FACC. Cedars-Sinai Medical Center, Los Angeles CA.

In 64 Pts with acute myocardial infarction of ≤3 hr duration, the residual serum fibrinogen following 750,000 U IV streptokinase (SK) correlated directly (r=0.58,p<.001) with the time interval from initiation of treatment to reperfusion (REP). Reperfusion was achieved in 35±21 min in all 41 Pts with a fibrinogen of ≤50 mg% (23±11 mg% at 74±44 min post-SK). In contrast, of the 23 Pts with a fibrinogen of >50 mg% (108±64 mg% at 89±54 min post-SK), REP was not achieved in 4 Pts and was delayed for 67±39 min in the remaining 19 Pts (p<0.001 vs Pts with FIB of ≤50 mg%). All 5 Pts with a fibrinogen of >90 mg% in whom the pretreatment anti-SK antibody titer was measured had very high titers suggesting that in these Pts, the high fibrinogen and the delay or failure of reperfusion were due to inactivation of a significant portion of the SK dose by anti-SK antibodies. Pretreatment with 40 U/Kg IV heparin significantly shortened SK-REP in the 17 Pts with fibrinogen of ≤50 mg%, but not in the 9 Pts with a residual fibrinogen of >50 mg% (Table). Symptom duration and IV-SK infusion rate were comparable in all 4 groups.

*p<0.01.	FIBRINOGEN ≤ 50 mg% Heparin n=17	FIBRINOGEN ≤ 50 mg% No Heparin n=24	FIBRINOGEN > 50 mg% Heparin n=9	FIBRINOGEN > 50 mg% No Heparin n=10
SK-REP (min):	24±9*	42±23*	70±45	65±34

Our data suggest that: 1) Reperfusion following IV-SK is delayed or may not occur when the residual fibrinogen is high, probably due to substantial inactivation of the SK by preexisting antibodies. 2) In patients in whom IV-SK markedly depletes fibrinogen, pretreatment with heparin significantly shortens the time interval to reperfusion.

WHICH PATIENTS BENEFIT MOST OF THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION ?

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To study the effect of thrombolysis (T) 533 pts were randomly allocated to conventional treatment (C, 264 pts) or intracoronary streptokinase (IC SK, 152 pts) or IC SK preceded by 500.000 U SK intravenously(IV+IC SK, 117 pts). Baseline characteristics were similar in both groups, including the sum of ST elevations at admission (SST) and duration of symptoms before hospital admission.
T was associated with a 30% smaller infarct size as estimated from total myocardial HBDH release ($p < 0.0001$). Limitation of infarct size was greater in pts admitted within 2 hrs (41%) than in pts arriving after 2-4 hrs (18%); in pts with SST ≥12mm (35%) than SST <12 mm (30%); in pts treated with IV + IC SK (39%) than with IC SK only (27%). Mean left ventricular ejection fraction (LVEF) before discharge was 5% higher in T compared to C (49% and 44%, $p < 0.001$). Differences in LVEF were greater in pts with SST ≥12mm (6%) than in pts with SST <12 mm (4%) and in pts arriving within 2 hrs (7%) than in pts arriving after 2-4 hrs (3%). In the subgroup of 68 patients with STT < 12 mm and arriving after 2-4 hrs no differences were found in infarct size and LVEF between C and T.
Multivariate analysis confirmed that the interval between onset of symptoms and hospital admission, and SST were independently related to the limitation of infarct size and the improvement of LVEF by thrombolysis.
Early thrombolysis by IC + IV SK limits infarct size and improves left ventricular function, particularly in pts with extensive myocardial ischemia (SST ≥12 mm) and in pts hospitalized within 2 hrs after onset of symptoms.

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Monday, March 10, 1986
4:00PM–5:30PM, Room #264/265/266
Thrombolysis II

EARLY THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION (MI): REDUCTION OF INFARCT SIZE, PRESERVATION OF LEFT VENTRICULAR FUNCTION AND IMPROVED SURVIVAL.

Maarten L. Simoons, M.D., F.A.C.C., Patrick W. Serruys, M.D., Marcel v/d Brand, M.D., Frits Bär, M.D., Chris de Zwaan, M.D., Jan Res, M.D., Freek W.A. Verheugt, M.D., X. Hanno Krauss, M.D., Willem J. Remme, M.D., Frank Vermeer, M.D., Jacobus Lubsen, Ph.D.
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A randomized trial comparing early (less than 4 hours after symptoms of myocardial infarction) thrombolysis (T) by intracoronary (ic) or intravenous (iv) followed by ic streptokinase with conventional therapy (C) was completed in March 1985. 533 patients (pts) with MI were randomized, 264 C and 269 T. All baseline data were similar. 35 pts allocated to T did not accept the intervention. At the end of the procedure the infarct related artery was patent in 198 pts (85%) and remained occluded in 36 pts allocated to T. Median time until recanalisation was 200 minutes.
In hospital course was more favorable after T : cardiogenic shock 24 C, 13 T (p=0.08), ventricular fibrillation 61 C, 38 T (p=0.01), pericarditis 46 C, 19 T (p=0.0004), although bleeding was more frequent (53 T, 7 C, p=0.0001). Infarct size estimated from serial enzyme release was 30% lower after T. Global left ventricular function measured by radionuclide angiography before discharge was better after T than in C (48±15% vs 44±15%, p=0.003). Mortality was lower after T, both at 28 days (16 T, 31 C) and at one year median follow up (42 C, 23 T, p=0.01) although reinfarction occurred more frequent after T (16 C, 36 T, p=0.004), in particular in patients with inferior MI.
Early thrombolysis does lead to substantial limitation of infarct size, preservation of left ventricular function and improved survival. Since reinfarction occurs more frequently after thrombolysis further studies should address measures to prevent this complication.

PERSISTENT IMPROVEMENT OF LEFT VENTRICULAR FUNCTION IN A RANDOMIZED CONTROLLED TRIAL OF RECANALIZATION: FINAL REPORT

Jan C.J. Res, M.D., F.W.A. Verheugt, M.D., E.E. van der Wall, M.D., M.J. van Eenige, M.S.E.E., M.L. Simoons, M.D., F.A.C.C., C. de Zwaan, M.D., S. Braat, M.D., W.J. Remme, M.D., F. Vermeer, M.D., Interuniversity Cardiology Institute, The Netherlands

To assess the effect of recanalization on left ventricular ejection fraction (LVEF) radionuclide angiography was performed in 533 patients (pts) with acute myocardial infarction (MI) enrolled in a randomized controlled trial comparing conventional treatment (C, 264 pts) with intracoronary streptokinase (SK, 269 pts). Pretreatment with intravenous SK was done in 117 pts. In 416 pts first MI was diagnosed, 117 had previous MI. LVEF was measured at day 1-3, at 2 weeks and at 3 months after MI. Within 3 months 34 C and 18 SK pts died. Paired data (ΔLVEF) were obtained:

	day 1-3→2 weeks		day 1-3→3 months	
mean ± SD	C (n=115)	SK (n=161)	C (n=115)	SK (n=139)
all	1 ± 11	4 ± 9*	2 ± 13	4 ± 12*
anterior MI	1 ± 9	5 ± 9*	3 ± 10	6 ± 13°
inferior MI	1 ± 13	3 ± 9°	1 ± 14	2 ± 11
first MI	1 ± 12	4 ± 9*	2 ± 13	3 ± 12°
previous MI	-1 ± 7	4 ± 9	0 ± 10	5 ± 13

* p <0.0001 •p <0.001 °p <0.01

Recurrent MI within 3 months occurred in 8 C pts (5 ant MI, 3 inf MI, ΔLVEF -7 and -14% resp) and in 17 SK pts (4 ant MI, 13 inf MI, ΔLVEF 5 and -1% resp).
Thus, persistent improvement of LVEF by SK is seen in particular in first and anterior MI. Improvement of LVEF by SK in inferior MI is partly abolished by the higher incidence of recurrent MI.

PRESERVATION OF MYOCARDIAL FUNCTION IN THE INFARCT ZONE. FINAL REPORT OF THE DUTCH MULTICENTER RANDOMIZED TRIAL ON INTRACORONARY THROMBOLYSIS.

Patrick W Serruys, MD, Maarten L Simoons, MD, FACC, Haryanto Suryapranata, MD, Frank Vermeer, MD, William Wijns, MD, Marcel vd Brand, MD, Frits Bär, MD, Chris de Zwaan, MD, X Hanno Krauss, MD, William J Remme, MD, Jan Res, MD, Freek WA Verheugt, MD, Ronald van Domburg, MS, Jacobus Lubsen, MD, Paul G Hugenholtz, MD, FACC.
The Netherlands Interuniversity Cardiology Institute.

Between June 1981 and March 1985, 533 pts with AMI were enrolled within 4 hours of onset of symptoms in a randomized trial of intracoronary thrombolysis (TR, n=269 pts) with streptokinase versus conventional treatment (CT, n=264 pts). Median time between onset of symptoms and recanalization was 200 min and the infarct related patency was 85%. LV angiography was available prior to discharge in 332 pts (174 CT, group I, 158 TR gr II). In gr II a subset of 46 pts (gr III) were recanalized within 180 min. The regional contribution of the infarct zones (CREF-IZ %) to the global ejection fraction (EF %) were assessed in 4 LV regions: AB,IB=antero, infero basal; AA, IA=antero, infero apical. Results as mean ± SD

	EF	CREF AB	CREF AA	CREF IB	CREF IA
I	47±14	12.2±4.1	4.4±3.1	10.8±4.7	6.9±4.1
II	53±13*	14.0±3.6"	5.6±3.4"	12.6±4.3"	9.5±3.3*
III	57±11*	14.4±3.9'	6.0±3.7°	13.6±4.3"	10.9±3.3*

° p < .02 ' p < .01 " p < .005 * p < .0001 versus gr I.

Analysis following the intention-to-treat principle (gr I and II) demonstrates that TR reduces the loss of functional myocardium in anterior as well as in inferior MI. This beneficial effect is particularly evident when recanalization is achieved within 3 hours (Group III).

SEQUENTIAL INTRAVENOUS THROMBOLYSIS AND CORONARY ANGIOPLASTY VS. DIRECT PTCA THERAPY FOR ACUTE MYOCARDIAL INFARCTION.

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The optimal approach to achieve myocardial infarct (MI) vessel recanalization remains undefined. We compared sequential therapy (S) of intravenous thrombolysis (streptokinase 1.5 mill U) and emergency PTCA in 31 patients vs. direct (D) PTCA in 29. The 2 groups were similar with respect to demographic parameters, infarct location, and time from onset of chest pain to PTCA. All patients received IV heparin, aspirin + dipyridamole for 1 wk. Infarct vessel patency was defined as rapid flow and clearance of contrast (TIMI Grade 3); bleeding as requiring transfusion, or resulting in significant morbidity. Follow-up cardiac catheterization at 1 week post-MI was obtained in 49/60 patients. A repeat LV gram was used to determine the change (Day 7 to Day 0) in ejection fraction (ΔEF).

	S (N=31)		D (N=29)		P
Initial Patency	16	61%	4	13%	.002
Post-PTCA Patency	27/28	96%	24/29	83%	.09
1 Week Patency	25/26	96%	20/23	86%	NS
Bleeding	7	22%	9	31%	NS
ΔEF ($\bar{x}$±SD)	↑8.1±10		↑7.7±7		NS

We conclude: (1) Similar results were obtained with sequential vs. direct PTCA therapy with respect to global LV function, and 1 wk follow-up infarct vessel status; (2) the comparable incidence of significant bleeding episodes in the 2 groups suggests that invasive punctures, heparin and antiplatelet agents are more important than fibrinolytic therapy in causing hemorrhage.

LONG TERM FOLLOW-UP OF PATIENTS RECEIVING INTRACORONARY STREPTOKINASE COMPARED WITH RANDOMLY ASSIGNED CONTROLS.

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We collected long term follow-up data (27 ± 14 months) on 100% of a cohort of 83 consecutive acute infarct (AMI) pts either treated with intracoronary streptokinase or randomly assigned to a control group also undergoing immediate coronary angiography. Time from AMI symptoms onset to treatment was <5h. Outcome analysis was by infarct artery patency (PAT) n=42 or occlusion (OCC) n=41, 90 min after start of angiography. Tabulated are mortality (all but one death[*] known or suspected to be cardiac) and recurrent ischemic events (angina or reinfarct), in hospital, after discharge but within 1 year ("1st yr"), and beyond 1 yr (>1 year).

	All Cause Mortality			Recurrent Ischemia		
	Patent	Occluded	p	Patent	Occluded	p
In Hosp	0 pts	2 pts	ns	20 pts	3 pts	<.001
1st Year	4 pts	4 pts	ns	11 pts	7 pts	<.02
>1 Year	2 pts	2*pts	ns	2 pts	7 pts	ns
Total	6 pts	8 pts	ns	33 pts	17 pts	<.05

Mean discharge ejection fractions in PAT and OCC groups were identical (45%±14 vs 45%±15, respectively) but was lower in those who died during follow-up (38%±14) than for survivors (47±14, p<.05). PTCA or CABG was more often required in PAT pts, 17/42 (40%), than in OCC pts 8/41 (20%), p<.05. Conclusions: 1) Early and long term survival was unaffected by infarct artery patency; 2) Early recurrent ischemic events were common when the infarct artery was reperfused, often necessitating mechanical intervention.

Monday, March 10, 1986
2:00PM–3:30PM, Room #260/261
Angioplasty: Indications and Results

RESTENOSIS AND LATE CARDIAC EVENTS AFTER SUCCESSFUL CORONARY ANGIOPLASTY IN ELDERLY PATIENTS.

Pierre Abi-Mansour, M.D., Gary Roubin, M.B., Ph.D., Claire Rice, R.N., Clayton Bredlau, M.D., John Douglas, M.D., Spencer King, M.D., Andreas Gruentzig, M.D., F.A.C.C. Emory University School of Medicine, Atlanta, Georgia.

PTCA can be performed in patients (pts) older than 65 years with low morbidity and mortality but the late outcome and restenosis rate in these pts is unknown. To determine the influence of PTCA on survival and cardiac event rate, we prospectively followed 131 consecutive pts older than 65 years (age=69±3 years, mean±SD) who had successful PTCA at Emory University between 1/1/81 and 12/31/82. 72% were male and 28% female. The incidence of multivessel disease was 17%, previous myocardial infarction (MI) 23% and prior bypass surgery (CABG) 8%. The majority of pts (56%) had unstable angina pectoris. Repeat coronary angiography was available in 101 pts (77%) at a mean time of 8±7 months. Of these, 37 (36%) had restenosis(RS). 11 of 37 were maintained on medical therapy, 5 had CABG, and 21 had repeat PTCA. Repeat PTCA was successful in 20/21 pts (95%) but 5 of these subsequently required CABG because of RS or disease progression at another site. 2 additional pts who did not have RS had PTCA for disease progression at a different site. At late mean follow-up of 30±10 months (range 12-52 mo.), 2 pts died from noncardiac causes (malignancy), there were no cardiac deaths and no MI and 115/131 pts (88%) were asymptomatic or improved without undergoing CABG.

Conclusion: In elderly pts the restenosis rate after PTCA is similar to that reported in younger pts. Successful PTCA offers older patients extended effective therapy with excellent short term survival and a low risk of subsequent cardiac events.

STATE OF THE INFARCT RELATED CORONARY ARTERY IMMEDIATELY AND 3 DAYS AFTER SUCCESSFUL INTRACORONARY THROMBOLYSIS WITH STREPTOKINASE.

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In 365 (79 %, group 1) out of 461 patients (pts) with acute myocardial infarction, the first angio revealed a complete thrombotic obstruction; 96 pts (21 %, group 2) had a high degree of stenosis of the infarct related coronary artery. The remaining stenosis immediately after successful intracoronary (ic.) thrombolysis with Streptokinase (SK) was assessed quantitatively in 140 consecutive pts (n = 106 out of group 1, n = 34 out of group 2) using at least 2 angiographic projections. A 2nd angio was obtained 3 days later before removing the introducer sheet. The influence of total time of occlusion and of the anatomy of the lesion (initially complete or incomplete obstruction, length, excentricity) on the development of the residual stenosis was analysed; within the observation period, no mechanical intervention (PTCA, bypass surgery) took place. 2 – 6 mg of nitroglycerin / h and 25.000 – 35.000 U of heparin / 24 hs were administered continously.

TIME AFTER LYSIS	GROUP 1		GROUP 2		
	DIAMETER	CROSS SECT.	DIAMETER	CROSS SECT.	
Immediately	70.7 ± 9.5	90.4 ± 6.1	69.7 ± 7.2	90.2 ± 5.0	*
3rd day	65.8 ± 13.7	86.3 ± 10.6	65.8 ± 14.1	86.3 ± 12.4	*
	ns			* p<0.0001	

In only 8 pts, the improvement exceeded 20 % of diameter, whereas the degree of stenosis remained unchanged (< 10 % variation) in 111 cases, or even increased in 5 pts. Excentric stenoses decreased with an average of -6.8 ± 11.3 %, concentric with -3.5 ± 8.1 % of diameter (ns). Lesions ≤ 5 mm of length showed an improvement of -6.0 ± 7.1 %, >5 and ≤ 10 mm of -4.6 ± 9.9 %, and >10 mm of -3,6 ± 10.2 % (ns). There was no correlation to total time of occlusion.

Thus, despite a slight but significant reduction, the residual stenosis 3 days after successful thrombolysis is still of hemodynamic importance in the majority of pts. The amount of increase or decrease of narrowing cannot be predicted from the anatomy of the lesion, and selected pts should be referred to PTCA or bypass surgery as soon as possible.

CORONARY ANGIOPLASTY OF THE "CULPRIT LESION": AN ALTERNATIVE APPROACH IN THE MANAGEMENT OF UNSTABLE ANGINA WITH MULTIVESSEL DISEASE.

Daniel Wohlgelernter, MD, FACC; Henry A. Highman, PA; Michael Cleman, MD. Yale University, New Haven, CT.

We sought to test the hypothesis that PTCA of the angina-producing vessel or "culprit lesion" can be effective therapy for selected pts. with unstable angina (UA) and multivessel coronary artery disease (MVD). The immediate and late follow-up results were analyzed in 20 pts. with MVD and UA refractory to medical therapy who underwent PTCA limited to the presumed angina-producing vessel. MVD was defined as ≥70% stenosis in two or more major coronary arteries. The culprit lesion was identified by angiographic morphologic features and localizing reversible ischemic ST changes on ECG obtained during episodes of angina. Angiographic characteristics used to identify the culprit lesion included: a) the presence of intracoronary thrombus; i.e., visualization of a filling defect outlined by contrast medium adjacent to a high-grade stenosis - 6 pts.; b) irregular, ragged margins of the area of stenosis, suggestive of plaque fissuring - 6 pts.; c) sub-total obstruction in one vessel with no other stenosis greater than 70% - 8 pts. All pts. had successful and uncomplicated PTCA (92% ± 6% - stenosis pre-PTCA, 11% ± 15% residual stenosis) with immediate resolution of UA. Follow-up after PTCA ranged from 8-19 months (mean - 11 months), and 18 of 20 pts. (90%) remain asymptomatic, with no angina or ischemic ECG changes on maximal treadmill testing. One pt with recurrent angina had restenosis of the dilated lesion documented by angiography. The other pt with angina post-PTCA had no evidence of restenosis. We conclude that single-vessel PTCA of the "culprit lesion" should be considered a therapeutic option for selected pts. with UA and MVD.

RECURRENT STENOSIS AFTER CORONARY ANGIOPLASTY.
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Recurrent stenosis (RS) after successful percutaneous transluminal coronary angioplasty (PTCA) remains a major problem with this method of revascularization. This study analyzed factors present at time of initial PTCA for their importance in RS. This study involved angiographic follow-up only; 634 segments in 536 patients. RS, defined as a recurrent stenosis at any site, was more common in multivessel PTCA (67.9%) than in single vessel single lesion (1-V, L) PTCA (37.8%). Multi-lesion PTCA performed in 1 vessel (37.7%) had no higher recurrence than 1-V, L PTCA (37.8%).

Analysis of 446 patients with 1-V, L PTCA showed diabetic (49.2% vs 36%) more likely to recur. No other risk factor correlated with recurrence. Patients with more severe disease (higher CHC) and lesion $\geq$90% also were more likely to recur. Patients left with a residual stenosis $\geq$40% were more likely to recur. Right coronary stenoses (22.1%) recurred less frequently than left anterior descending (45.2%) or circumflex (42.9%). The presence of intimal tear at PTCA site immediately after PTCA is associated with a lower recurrence rate (29.7% vs 40.4%).

PTCA is associated with a higher recurrence rate in diabetics, pts with severe disease, and left coronary artery lesion. Intimal tearing is desirable and may lower recurrence rate. Recurrence in multivessel PTCA is higher than 1-vessel, one lesion PTCA and appears to be cumulative.

FACTORS PREDICTING RECURRENCE IN PATIENTS WHO HAVE HAD ANGIOPLASTY (PTCA) OF TOTALLY OCCLUDED VESSELS
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In our series of 100 patients with totally occluded coronary arteries without evolving infarction, 124 patients had successful PTCA with a reduction of percent diameter stenosis (PDS) from 100% before to a mean (m) of 26% and range (r) of 8 to 63% after PTCA and change of pressure gradient (P) from m=50 mmHg (r=30-80) before to m=8 mmHg (r=0-20) after PTCA. 97 of these 124 patients have been followed for at least 6 months. Of these 97, 45 have had repeat angiography. 20 had patent vessels, 10% of whom were symptomatic (false positive). 25 demonstrated partial or total recurrence, 28% of whom were asymptomatic (false negative). Age, sex, diabetes, rest/nocturnal angina, duration of occlusion, PDS and P pre- and post-PTCA balloon inflation pressure (BIP) and number of inflations (I) were evaluated to assess predictors of recurrence. Logistic regression analyses demonstrated that recurrence was more likely to occur in: 1) patients with lesions requiring more I ($p<.05$); and 2) lesions requiring higher BIP ($p<.05$). In summary, clinical symptoms (angina) may not be a reliable index of recurrence, but lesions requiring more I and higher BIP may be more likely to recur following PTCA of recent total occlusions.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN PATIENTS WITH PRIOR MYOCARDIAL INFARCTION.
Michael Savage, M.D., John P. Dervan, M.D., Andrew Zalewski, M.D., Sonya Slysh, M.D., James Hopkins, M.D., Sheldon Goldberg, M.D., F.A.C.C. Thomas Jefferson University Hospital, Philadelphia, PA

Patients undergoing percutaneous transluminal coronary angioplasty (PTCA) who have had a prior transmural myocardial infarction (MI) in the distribution of another coronary artery are properly considered a high-risk group because of potential severe LV dysfunction if an acute ischemic complication occurs. Accordingly, to evaluate the safety and efficacy of PTCA in this setting, 225 consecutive patients undergoing PTCA were divided into: 19 patients (Group I) who had a prior MI remote from the artery undergoing PTCA, and 206 patients (Group II) with no remote MI. All patients in Group I had pathologic Q-waves on ECG and/or segmental akinesis on ventriculography. PTCA outcome for Groups I and II were as follows:

Group	Pre-PTCA Stenosis(%)	Post-PTCA Stenosis(%)	Gradient (mmHg)	Primary Success(%)
I	91±6	29±18	7±5	90%
II	94±5	39±27	11±6	84%
p	NS	NS	NS	NS

Mean severity of stenosis and translesional gradient post-PTCA were similar in both groups. Furthermore, primary success (i.e., residual stenosis $\leq$50%) was comparable in the two groups. There was no difference in frequency of acute ischemic complications requiring emergency coronary bypass surgery (Group I-2 patients, Group II-10 patients; NS). Importantly, there were no deaths in either group. We conclude: (1) PTCA is a suitable therapeutic procedure in selected patients with underlying LV dysfunction due to prior MI remote from the site of angioplasty, (2) with immediate operating room standby, PTCA can be performed successfully in such patients with low morbidity and mortality.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY FOR EARLY POSTINFARCTION UNSTABLE ANGINA; RESULTS AND FOLLOW-UP.
Sidney O. Gottlieb M.D., Kenneth P. Brin M.D., Ph.D., F.A.C.C., Gary D. Walford M.D., Mark McGaughey M.D., Mary Beth Riegel R.N., and Jeffrey A. Brinker M.D., F.A.C.C. The Johns Hopkins Medical Institutions, Baltimore, MD.

Unstable angina (UA) occurring in the early post-infarction (post-MI) period is associated with an increased incidence of unfavorable cardiac events despite aggressive medical therapy. We examined the results of coronary angioplasty (CA) in 47 consecutive patients (pts) with post-MI UA, who were referred for CA 12.9 ± 7 days following MI (14 transmural, TM, and 33 non-TM). CA was performed on 55 arteries with a mean stenosis of 95 ± 8%. These included 46 infarct-related arteries, and 9 non-infarct arteries. Double vessel CA was performed in 8 pts. Successful CA was achieved in 43 pts (91%), with a mean residual stenosis of 33 ± 28%. There was no operative mortality, and follow-up for a mean of 7.5 months revealed 1 cardiac death, 2 myocardial infarctions, and 3 had surgical revascularization. Repeat CA was required in 6 pts from 2-105 days after initial CA, and was successful in 5 pts (83%). Of the 40 pts who had a successful PTCA and were discharged from the hospital without an unfavorable outcome, 31 (78%) remain angina-free over the average follow up period of 7.5 months. The presence of either clot or coronary artery dissection were not predictive of subsequent unfavorable outcomes. Thus CA offers a low-risk efficacious therapeutic option for selected pts with early post-MI unstable angina.

Monday, March 10, 1986
4:00PM-5:30PM, Room #260/261
The Results of Angioplasty

FRENCH PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) REGISTRY : FOUR YEARS EXPERIENCE.

Michel E. Bertrand, M.D., Jean Marco, M.D., François Cherrier, M.D., R. Schmitt, M.D., Ph. Gaspard, M.D., J. Puel, M.D., B. Valeix, M.D., M. Bory, M.D., H. Crochet, M.D., H. Geschwind, M.D., R. Berland, M.D., J. Machecourt, M.D., J.P. Foucault, J.P. Bassand, Cl. Bourdonnec, A. Quiret, F. Jault.

Data collected on 3198 patients (pts) undergoing PTCA in 17 French institutions during the past 4 years have been analyzed regarding the effectiveness and mid term results of PTCA. The patients were subdivided in two groups : Group A (n = 2385) with single vessel disease. Group B (n = 813) with multiple vessel disease

	Group A	Group B
Crossed stenosis	88%	88%
Primary success	73%	78%
Death	0.9%	2.2%
Myocardial infarction	5.2%	5.8%
Emergency CABG	4.1%	4.5%
Negative ex. test post PTCA	85%	74%

The patients were restudied 7.7 months and 5 months later respectively in Group A and Group B.
At the time of reinvestigation 71% in group A and 65% in group B were free of symptoms. Exercise test was negative in 75% and 65% respectively. Restenosis, defined as a loss of at least 50% of the initial gain was observed in 31% (group A) and 34% (group B). Thus, success rate was similar in both the 2 groups but the risk of mortality was higher in the group with multiple vessel disease (group B)

DISEASE PROGRESSION AFTER CORONARY ANGIOPLASTY (PTCA): RELATION TO VESSEL INSTRUMENTATION

Kevin Nugent, B.S., Gary Roubin, M.B., Ph.D., Stephen Ellis, M.D., Andreas Gruentzig, M.D., F.A.C.C. Emory University School of Medicine, Atlanta, Georgia

To determine if disease progression is accelerated by vessel instrumentation during PTCA, we studied pre-PTCA and follow-up arteriograms in 86 patients (pts) with 90 dilation sites who had repeat angiography at least 12 months (mean 21+7 months) after PTCA. Luminal diameter stenoses in dilated and non-dilated segments of all diseased vessels were measured using digital calipers. Restenosis (RS) was defined as a $\geq$50% diameter stenosis at the dilation site. Intraobserver variability demonstrated a mean difference of 4.1 percentage points (range 0-13) in 71 randomly selected lesions. Disease progression was thus defined as an increase in diameter stenosis of $\geq$15 percentage points in any non-dilated vessel segment.

Restenosis was present in 24 of 86 (28%) patients. Disease progession occurred with similar frequency in patients with restenosis and continued success: 15/24 (62%) vs 40/62 (64%). Disease progression also occurred with similar frequency in dilated and non-dilated vessels. Progression was observed in 36 of 422 (8.7%) non-dilated segments of dilated vessels and in 64 of 864 (7.4%) of segments in the non-dilated vessels (p=NS).

We conclude that: 1) instrumentation during PTCA does not accelerate disease progression in the dilated vessel, and 2) late restenosis after PTCA is not related to progression of native disease.

LATE RECURRENCE OF ANGINA FOLLOWING CORONARY ANGIOPLASTY: THE ROLE OF NEW ATHEROSCLEROTIC DISEASE.

Edward W. Robert, M.D., F.A.C.C., William B. Ricks, M.D., F.A.C.C., Ronald M. Rossen, M.D., F.A.C.C., Michael R. Nagel, M.D., F.A.C.C., Stephen E. Green, M.D., F.A.C.C., Ada Koransky, M.D., and Terry Thomas, R.N., Good Samaritan Hospital, San Jose, California.

To study the etiology of the late recurrence of angina after coronary angioplasty (PTCA), we retrospectively analyzed a cohort of 25 patients (pts) who developed evidence for myocardial ischemia and underwent repeat coronary arteriography following a post-PTCA symptom-free interval of more than 6 mos (LR). Results were compared with a group of 47 pts (53 initially successful procedures) who developed recurrent ischemia within 6 mos of PTCA (ER). Indications for angiography in the LR vs ER groups were asymptomatic positive treadmill (4% vs 17%), atypical chest pain (12% vs 4%), recurrent stable angina (44% vs 49%), unstable angina (24% vs 23%), and acute myocardial infarction (16% vs 4%). In the LR group, recurrence at the dilation site occurred in 7 (28%) vs 39 (74%) in the ER group ($p<0.001$). New atherosclerosis occurred in 10 (40%) of the LR group vs 3 (6%) of the ER group ($p<0.001$). In the LR group, 2 of 7 pts with recurrence had thrombus rather than atherosclerotic restenosis and 1 restenosis accompanied a more critical new stenosis. Of the 10 pts with new disease, 7 demonstrated progression in a non-dilated vessel and 2 in the proximal portion of the dilated vessel. Within LR, atherosclerotic restenosis occurred earlier (mean 11.0 mos) than new atherosclerotic disease (mean 18.0 mos) ($p<0.05$). We conclude that restenosis is unusual more than 6 mos after PTCA and that late (>6 mos) recurrence of myocardial ischemia is more commonly associated with new atherosclerotic disease.

LATE RESULTS OF MULTIPLE LESION CORONARY ANGIOPLASTY IN AN AGED POPULATION.

Geoffrey O. Hartzler, M.D., FACC, Barry D. Rutherford, M.D., FACC, David R. McConahay, M.D., FACC, Warren L. Johnson, Jr., M.D., FACC, Bob Ligon, M.S., and Martha Calkins, R.N., Mid America Heart Institute, St. Luke's Hospital, Kansas City, Missouri.

The long-term results of multiple lesion PTCA in elderly patients have not yet been characterized. Of our first 500 consecutive multiple lesion PTCA procedures between August 1980 and July 1983, 72 were performed in patients 70 years of age or older. There were 45 males and 27 females with ages ranging 70-82 yrs, mean age 74 yrs. From 2-7 stenoses were dilated (total 206 lesions, 2.86/pt) with 89% primary success. Complications included myocardial infarction - 2 pts (2.8%) and urgent bypass surgery - 3 pts (4.2%). There were 4 procedure-related deaths for a mortality of 5.6%. Of 66 pts available for followup at 1.6-4.2 yrs (m = 2.3 yrs), there were 3 MIs (4.5%), 6 CABGs (9%), and 8 deaths (12%). Eight pts (12%) underwent repeat PTCA at 2-12 mos (m = 8 mos) for isolated restenosis in 3 pts, restenosis and new lesions in 4 pts, and new lesions in 1 pt. At followup, 91% of patients reported symptomatic improvement since PTCA.

Conclusion: Multilesion PTCA in the aged population is associated with increased procedural risk. The annual post-procedure incidence of myocardial infarction and cross-over to CABG is low. The increased mortality at followup in this early series of elderly patients mandates continued evaluation and caution in the application of angioplasty to this subgroup.

RESTENOSIS AFTER MULTI-LESION AND MULTIVESSEL CORONARY ANGIOPLASTY (PTCA).

Gary Roubin, M.B., Ph.D., Douglas Redd, M.S., Pierre Leimgruber, M.D., Pierre Abi-Mansour, M.D., Johnny Tate, Andreas Gruentzig, M.D., F.A.C.C. Emory University School of Medicine, Atlanta, GA.

To determine the relative incidence of lesion restenosis in patients undergoing multi-lesion (ML) and multivessel (MV) PTCA, we examined the late outcome in 411 patients (pts) who underwent ML or MV PTCA from October 1980 through January 1985. Multi-lesion pts (n=282) had 2 or more lesions dilated at different sites in the same coronary artery and multivessel pts (n=129) had 2 or more discrete lesions dilated in different coronary arteries. The time of arteriographic restudy, ML 7.2±5 months vs MV 7.3±5 months (mean±SD) and restudy rate ML 181/282 (64%) vs MV 86/129 (67%) were similar. Clinical characteristics: Females, ML 19% vs MV 12%; Age, ML 55±10 years vs MV 54±10 yrs, Duration of symptoms <2 months, ML 28% vs MV 33% and initial results - Diameter stenosis post-PTCA, ML 23±11% vs MV 25±11% and gradient post PTCA, ML 13±7mmHg vs MV 12±6mmHg were also comparable. Restenosis rate per patient was 90/181 (50%) in multilesion pts vs 30/86(35%) in multivessel pts ($p < 0.05$) and restenosis rate per lesion was 118/372 (32%) in multilesion pts and 37/189 (20%) in multivessel pts ($p<0.005$).

We conclude that the risk of restenosis is strongly related to the number of dilatation sites if ML-PTCA is performed in one vessel. PTCA of multiple discrete lesions in different vessels is not associated with an increased risk of restenosis.

IDENTIFICATION AND CHARACTERIZATION OF CAUSES FOR RECURRENT ANGINAL SYMPTOMS FOLLOWING SUCCESSFUL CORONARY ANGIOPLASTY: THE RESULTS OF A FOLLOW-UP ANGIOGRAPHIC ANALYSIS John Joelson, M.D., Albert S. Most, M.D.,FACC, Steven Reinert, MS, David O. Williams, M.D., FACC, RI Hospital, Brown University, Providence, Rhode Island

The angiographic and clinical characteristics of 77 consecutive patients (PTS) who underwent follow-up coronary cineangiography for the assessment of recurrent chest pain following successful coronary angioplasty (CA) were reviewed to determine 1) the responsible mechanism for recurrent anginal symptoms, and 2) whether the mechanism could be correctly identified by certain clinical characteristics short of angiography. Based on angiographic findings, PTS were classified as having restenosis (RE: n=43), development of new, significant coronary disease (NEW: n=15), incomplete revascularization (IR: n=6) or no coronary disease (NL: n=13). Groups did not differ in terms of age, gender, number of dilations performed, peak inflation pressure or in the pre or post CA stenosis or gradient. Multivessel coronary disease was more common among those with NEW or IR ($P < .01$). The elapsed time from CA to onset of recurrent symptoms was the most powerful predictor of angiographic outcome.

Elapsed Time (months)	RE	NEW	IR	NL
< 1	1	0	4	6
≥ 1 ≤ 6	40	2	2	4
> 6	2	13	0	3

$P < 0.001$

Thus, PTS who experience recurrent chest pain following successful CA have variable angiographic findings. Restenosis is the most common observation. The time elapsed from CA to the onset of chest pain is of value in predicting angiographic findings. Hence, PTS who develop symptoms within one month usually demonstrate IR or NL. RE is the most common explanation for chest pain occurring within 1-6 months. Pain occurring after 6 months is usually due to development of new, significant CAD.

Monday, March 10, 1986
2:00PM-3:30PM, Room #360/361
Thallium 201: II. Quantitative Studies and SPECT

QUANTITATIVE ANALYSIS OF T1-201 MYOCARDIAL SINGLE-PHOTON EMISSION COMPUTERIZED ROTATIONAL TOMOGRAPHY: DEVELOPMENT, VALIDATION, AND PROSPECTIVE APPLICATION OF AN OPTIMIZED COMPUTERIZED METHOD. Jamshid Maddahi, MD, FACC; Kenneth Van Train, BS; Christopher Wong, CNMT; Florence Prigent, MD; Joshua Gurewitz, CNMT; John Friedman, MD; Daniel Berman, MD, FACC. Cedars-Sinai Med Ctr, Los Angeles, CA

To assess the ability of quantitative analysis of stress-redistribution T1-201 rotational tomography to detect and localize coronary artery disease (CAD), we studied 84 male patients, 41 normals (nls) (34 with <5% calculated likelihood of CAD and 7 with nl coronary arteries) and 43 with angiographic CAD (≥50% stenosis). All pts underwent stress-redistribution rotational tomography using 3 mCi of T1-201, obtaining 30-32 projections (30 seconds each) over 180°. After low-pass filtering, images were reconstructed into short- and vertical long-axis tomograms. For each tomogram, a maximum-count circumferential profile was generated, normalized to its maximum count and plotted onto a 2-dimensional polar coordinate map representing the entire myocardial distribution of T1-201. In a random pilot population of 15 low-likelihood nls and 15 CAD patients, nl limits for initial T1-201 distribution were developed as well as criteria for abnormality and a topographic scheme for automatic assignment of the various myocardial regions to coronary arteries. Subsequently, the developed criteria were applied prospectively to the remaining 54 pts (26 nls and 28 CAD's). Results:

	Overall	LAD	LCX	RCA
Sensitivity	23/28=.82	18/25=.72	18/21=.86	21/26=.81
Specificity	22/26=.84	22/29=.76	24/33=.76	24/28=.86

Conclusion: The described optimized acquisition, processing, and automatic interpretation approach to stress myocardial T1-201 rotational tomograms appears to be accurate for overall detection of CAD and identification of disease in individual coronary arteries.

QUANTITATIVE ROTATIONAL THALLIUM-201 TOMOGRAPHY FOR IDENTIFYING AND LOCALIZING CORONARY ARTERY DISEASE (CAD): BULLSEYE POLAR MAP. Eugene DePasquale, M.D. FACC, Agatha Nody, M.D. FACC, Gordon DePuey, M.D. FACC, Ernest Garcia, Ph.D., George Pilcher, M.D., Clayton Bredlau, M.D., Gary Roubin, MB, Ph.D., Robert Eisner, Ph.D., Anita Gober, Andreas Gruentzig, M.D. FACC, Harvey Berger, M.D. FACC, Emory University, Atlanta GA

To determine the accuracy of tomographic thallium-201 (Tl) imaging in localizing CAD, exercise (ex) studies were quantified using maximal count circumferential profiles in 291 patients (pts). Polar coordinate maps were constructed as a series of concentric profiles with the apex at the center and displayed as a functional image. Normal (nl) limits were established using 36 pts with low probability of CAD (<5%). 45 of the pts were used in a pilot study to determine the best criteria for identification and localization of perfusion defects; contiguous defects > 2.5 SD from mean nl were considered significant. These criteria were applied prospectively to the remaining 210 pts (179 pts with > 50% diameter stenosis (DS) and 31 with < 50% DS). 86/179 pts had multivessel CAD. DS was quantified by digital calipers. 278/630 vessels were abnl. The sensitivity and specificity of Tl for CAD detection were 94% and 91%, respectively. The positive (pos) and negative (neg) predictive values (PV) were:

	LAD(n=96)	LCX(n=78)	RCA(n=104)	LCX & RCA
Pos PV	80%	89%	87%	92%
Neg PV	82%	82%	89%	82%

In 25 vessels with subcritical lesions (45-49% DS), 84% were abnl in the appropriate vascular bed. Thus, quantitative analysis of rotational Tl tomographic images is a highly accurate technique for determining the location and severity of CAD.

FACTORS CONTRIBUTING TO ABNORMAL QUANTITATIVE TL-201 SCINTIGRAMS IN PATIENTS WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES: AN UPDATE. Donald R. Lilly MD, James Ryan MD, Denny D. Watson PhD, Robert S. Gibson MD, Joseph A. Gascho MD, FACC, George A. Beller MD, FACC. University of Virginia Medical Center, Charlottesville, Virginia

Blinded quantitative readings of exercise thallium (Tl-201) scintigrams (ExTl) from 380 pts who underwent both coronary angiography (angio) and ExTl between 3/78 and 9/81 were performed by 2 observers. Overall sensitivity for detecting pts with stenosis ≥50% (CAD) was 87% (252/290). Of the 90 patients with normal angio, 32 (36%) were interpreted as abnormal by uptake or washout criteria, or both. We reviewed the scans retrospectively to identify potential causes for these "false positives". Of these 32 pts, 3 had definite prior MI with segmental akinesis or dyskinesis, 2 had cardiomyopathy and 3 had 25-50% stenoses. Of the remaining 24 pts, isolated washout abnormality (n=6), upper septal thinning (n=4), upper posterolateral thinning (n=2), breast attenuation (n=2), and apical thinning (n=1) resulted in the abnormal readings. No explanation was apparent in the remaining 9 pts. Isolated washout abnormalities (IWA) without numerically significant defects lead to the correct identification of only 2/290(1%) pts with CAD and thus would not affect our overall sensitivity if IWA was eliminated. Thus, the majority of pts (23/32) with normal coronary arteries and abnormal quantitative Tl-201 scintigrams have either structural heart disease, subcritical stenoses, IWA or recognizable image artifacts. Improved specificity, without loss of sensitivity, would be achieved if IWA alone was not considered abnormal. Referral bias may be important in these pts who were nonrandomly referred for angio on the basis of symptoms or abnormal noninvasive test results.

IMPORTANCE OF THE SITE AND TECHNIQUE OF INTRAVENOUS THALLIUM INJECTION DURING EXERCISE.
Rami Gal, M.D., Imran Niazi, M.D. and Steven C. Port, M.D., F.A.C.C. University of Wisconsin, Mount Sinai Medical Center, Milwaukee, WI.

Neither the site nor the technique of intravenous thallium (Tl) injection during exercise has been emphasized as important. We prospectively analyzed the effects of randomly varying the site (antecubital or more peripheral vein) and technique (with or without a 15cc saline flush) in 51 patients during routine testing. Both the usual myocardial views and a view of the arm injected were acquired post-exercise (PEx) and 3 hrs later (3Hr). Arm uptake of Tl (ArmTl) was not seen after medial antecubital injections except in 1 case injected via a 24 hr old indwelling catheter. ArmTl was seen in 19/37 (51%) of peripheral injections, more commonly in the left arm (53%) than the right (32%). A saline flush did not reduce ArmTl after peripheral injections. No clinical variables correlated with ArmTl. A subgroup with ArmTl and no PEx perfusion defects had 32% fewer PEx (p=0.00009) and 17% fewer 3Hr (p=.08) net myocardial cts/pixel. In addition, myocardial thallium washout was significantly slower in those with ArmTl compared to those without ArmTl (p=0.009). We conclude that the site of Tl injection during exercise is of substantial clinical importance. Injections distal to the antecubital veins often result in substantial ArmTl which can seriously compromise myocardial statistics.

SEVERELY DEPRESSED LEFT VENTRICULAR FUNCTION: ROLE OF REST-REDISTRIBUTION THALLIUM-201 IMAGING TO PREDICT IMPROVEMENT AFTER CORONARY BYPASS.
TM Bateman, MD, FACC; RJ Gray, MD, FACC; LSC Czer, MD, FACC; MJ Raymond, BSN; CM Conklin, BSN; J Maddahi, MD; Y Charuzi, MD, FACC; ME Lee, MD; JM Matloff, MD, FACC; DS Berman, MD, FACC. Cedars-Sinai Med Ctr, Los Angeles, CA.

Because prognosis after coronary artery bypass graft (CABG) surgery is strongly predicted by the post-CABG left ventricular ejection fraction (LVEF), the likelihood of improvement in LVEF should be an important factor in the selection of pts with very low LVEF for CABG. We hypothesized that rest-redistribution thallium-201 (Tl), by detection of regions with resting myocardial ischemia, could identify these pts. We measured pre- and post-CABG LVEF by radionuclide ventriculography (RNV) in 10 pts (8 male; age 60±12 yrs) with prior myocardial infarction, unstable angina, and severely reduced pre-CABG LVEF (all ≤ 30, mean 23±7%). RNV was performed <3 wks pre-CABG and within 3 months post-CABG. All pts underwent 3 view rest-redistribution Tl within 3 weeks pre-CABG. Six pts demonstrated fixed Tl defects only, and pre- and post-CABG LVEF was unchanged (24±8% pre vs. 27±7% post; p=NS). Four pts had from 1-4 myocardial segments with reversible resting Tl defects; LVEF improved in these pts from 22±5% to 32±5% (p<0.05). In all pts with reversible defects, LVEF rose by at least 8 EF points, while this rise occurred in only 1/6 with only fixed defects. Regional wall motion improved post-CABG in the vascular territories with reversible Tl defects, accounting for improvements in LVEF. **Conclusion:** In pts with poor LVEF, the presence of reversible resting Tl defects can identify those most likely to have improved left ventricular function post-CABG.

REGIONAL VARIABILITY IN THE MYOCARDIAL CLEARANCE OF TL-201 AND ITS IMPORTANCE IN DETERMINING THE PRESENCE OF CORONARY ARTERY DISEASE. S. Kaul, MD, FACC, R.D. Okada, MD, FACC, G.M. Pohost, MD, FACC, C.B. Boucher, MD, FACC. Massachusetts General Hospital, Boston, MA

There are several limitations in using absolute myocardial clearance (CL) of Tl-201 (Tl) for the detection of coronary artery disease (CAD). Noncardiac factors such as peak exercise heart rate and blood level of Tl can affect the absolute CL of Tl. However, as all myocardial segments (S) in a heart are exposed to the same noncardiac factors, a relative difference in CL of Tl between S could reflect the presence of CAD. Accordingly we analyzed CL in 370 patients: Group I (n=45) had <1% possibility of CAD; Group II (n=44) had normal coronary arteries; Group III (n=281) had CAD. Although mean CL in 15 myocardial S in 3 views in Group I was 3.4±0.7 hrs, the variability between the slowest and fastest clearing S in the same heart was as much as 98%. This variability was systematic: 78% of slowest clearing S were basal while 53% of fastest clearing S were apical (p<0.01). When Group II and III patients were compared, based on Group I values, the absolute CL of Tl had a sensitivity and specificity of 92% and 16% respectively. However, when CL in a S was considered abnormal only if it was 98% slower than in the fastest clearing S in the same heart, sensitivity and specificity changed to 69% and 86% respectively (p<0.01). When the latter values were provided for logistic regression analysis, following the inclusion of an initial defect, the model chose CL at par with redistribution and lung:heart ratio for the detection of CAD. In conclusion: 1) there is significant regional variability in the myocardial CL of Tl even in normal subjects; and 2) when CL is considered abnormal after comparing with the fastest clearing S in the myocardium, its diagnostic utility significantly improves.

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Monday, March 10, 1986
4:00PM–5:30PM, Room #360/361
Radionuclide Cineangiography: Evaluation of Ventricular Function

IS THERE ABNORMAL CONTRACTILE RESERVE IN HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY? Julio F.Tubau,M.D., Jadwiga Szlachcic, M.D., Shimon Braun,M.D., Steven Henderson,N.T., Carol Vollmer, R.N., Barry M. Massie, M.D., FACC, VAMC and UCSF, San Francisco, CA

Several reports have suggested abnormal exercise (EX) response in some patients (PTS) with hypertension (HTN) and left ventricular hypertrophy (LVH). Therefore, we examined the response to supine bicycle exercise in 13 normals (NLS) and 40 HTN PTS using blood pool scintigraphy. All HTN PTS were studied after one month off therapy. Additionally, significant coronary disease was ruled out by multiple non-invasive tests in all subjects. Twenty-three HTN PTS had evidence of LVH by echocardiography, as estimated by their left ventricular mass index (>100 g/m^2). Contractile reserve was assessed by the ratio of peak systolic pressure (PSP) to end-systolic volume index (ESV), and the change in EF from rest to exercise (ΔEF). Seven HTN-LVH PTS had abnormal rest or ΔEF (abnl ΔEF).

	NLS	HTN	HTN/LVH	abnl ΔEF
EF R (%)	67±8	62±7	67±67	55±10*#°
EF EX (%)	82±6	73±7	75±8	59±6 *#°
PSP/ESV R($mmHg/ml/m^2$)	3.0±1.2	3.8±1.6	4.2±1.7	3.3±1.0
PSP/ESV Ex($mmHg/ml/m^2$)	8.5±3.0	7.3±4.0	6.5±2.5	3.8±0.8*
PSP EX (mmHg)	197±22	209±16	201±20	226±10*#
MAX WORKLOAD(kpm/min)	1130±180	853±200	680±220*	670±200*#
ESV EX (ml/m^2)	14±4	18±9	18±7	29±4*#°

* p < .01 vs NL; # p < .05 vs HTN; °p<.05 vs HTN/LVH

All PTS exercised to a similar pressure-rate product. PSP/ESV at rest was not different among all groups but increased less with EX in HTN-LVH PTS and only insignificantly in those with abnormal ΔEF. End-systolic wall stress (σ) at rest in (10^3 dyn/m^2) was significantly higher in abnl ΔEF PTS 83±11 compared to HTN-LVH 64±6, HTN 55±14 and NLS 54±15 (all p<.01), predicting the reduction in contractile reserve and exercise tolerance.

NONINVASIVE IDENTIFICATION OF HIGH-RISK CORONARY ARTERY DISEASE
Raymond J. Gibbons, M.D., F.A.C.C., Ian P. Clements, M.D., F.A.C.C., Andre C. Lapeyre III, M.D., Manuel L. Brown, M.D., and Alan R. Zinsmeister, Ph.D., Mayo Clinic and Foundation, Rochester, Minnesota.

The purpose of this study was to noninvasively predict left main and/or 3-vessel coronary artery disease (LM3VCAD) in a group of 681 patients who underwent both exercise radionuclide angiography (RNA) and coronary angiography. When important clinical, ECG, and RNA variables were considered, logistic regression analysis identified 7 variables as independently predictive of LM3VCAD:

Variable (in order of importance)	p
Magnitude of ST depression	<.0001
Exercise ejection fraction	<.0001
Exercise heart rate-blood pressure product	<.0001
Sex	.0001
Exercise end-systolic volume index	.001
Exercise/rest systolic pressure to end-systolic volume ratio	.01
METS of exercise	.02

Employing these variables, the patients were separated into low-, intermediate, and high-risk groups on the basis of their predicted probability (PRED PROB) of LM3VCAD:

Group	N	PRED PROB	Actual LM3VCAD (n)	LM3VCAD %
Low risk	216	<.2	20	9%
Intermediate risk	300	.2-.5	78	26%
High risk	165	>.5	117	71%

In conclusion, (1) when both the exercise ECG and RNA are considered, the risk of LM3VCAD can be estimated noninvasively. (2) In this study, the high-risk group, composed of less than one-quarter of the total group, contained more than one-half of all the patients with LM3VCAD.

IMPROVED LEFT VENTRICULAR FUNCTION AT REST AFTER CORONARY ARTERY BYPASS: EVIDENCE FOR SUBCLINICAL ISCHEMIA UNDER RESTING CONDITIONS.
Vasken Dilsizian, MD, Robert O. Bonow, MD, FACC, Charles L. McIntosh, MD, FACC, Michael Jones, MD, Richard O. Cannon, MD, FACC, Stephen L. Bacharach, PhD, Michael V. Green, MS and Steven M. Larson, MD, NHLBI, Bethesda, Md.

Successful coronary artery bypass surgery (CABG) improves exercise induced left ventricular (LV) dysfunction in pts with coronary artery disease (CAD), but the potential effect of improving LV function at rest remains controversial. To assess the influence of CABG on LV function at rest, we studied 31 CAD pts without previous infarction before and 6 mos after CABG by radionuclide angiography after all cardiac medicines were withdrawn. No pt had angina at rest. In 27 pts with patent bypass grafts, CABG significantly increased LV ejection fraction (EF) during exercise (47±11% preop to 63±9% postop, p<.001), indicating reduction in reversible LV ischemia. Moreover, LVEF at rest increased (55±9 to 60±8%, p<.001), with 20 of 27 pts manifesting an increase compared to preoperative values: 12 of these 20 pts had apparently normal LV function at rest (EF and regional wall motion) before CABG. LV regional EF was computed by dividing the LV region of interest into 20 sectors. Regional analysis indicated that improved EF at rest after CABG occurred in those regions developing ischemia during exercise before CABG. In 4 pts with occluded grafts, EF at rest was unchanged by CABG globally (61±8 to 60±10%, p=NS) and regionally. Thus, LV global and regional function at rest improved after successful CABG, even in pts with apparently normal LV function before CABG. These data support the concept that many CAD pts have subclinical LV ischemia under resting conditions which is reversible after interventions that restore coronary flow.

ADHERENCE TO RADIONUCLIDE ANGIOCARDIOGRAPHIC GUIDELINES REDUCES THE INCIDENCE AND SEVERITY OF CONGESTIVE HEART FAILURE IN HIGH RISK PATIENTS: THE YALE DOXORUBICIN CARDIOTOXICITY STUDY. Ronald G. Schwartz, MD, Jonathan Alexander, MD FACC, William B. McKenzie, MD, Philip T. Sager, MD, John Setaro, MD, Peter E. Schwartz, MD, Frans J. Th. Wackers, MD FACC, Harvey J. Berger, MD FACC, and Barry L. Zaret, MD FACC. Yale University, New Haven, CT.

To assess the efficacy of our guidelines of serial resting radionuclide angiocardiography (RNA) to prevent congestive heart failure (CHF) due to doxorubicin (D), we compared guideline adherence to the incidence and severity of CHF in high risk patients. We recommend serial RNA prior to initiating D, after 250-300 mg/m^2, after 400-450 mg/m^2, and prior to subsequent doses. Termination of D is recommended if the left ventricular ejection fraction (LVEF) declines from a normal baseline (≥50%) by ≥10% (LVEF units) to ≤50%. With abnormal baseline LVEF, RNA prior to each dose is recommended with discontinuation of D when LVEF falls ≥10%, or to ≤30%.

	GUIDELINES FOLLOWED (N=48; 17%)	GUIDELINES NOT FOLLOWED (N=234; 83%)
CHF	2 (100% mild CHF)	44 (43% mild CHF; 57% mod/severe CHF)
NO CHF	46	190

Patients managed in accordance with the guidelines had a lower incidence of CHF (4.2%) than those who were not (18.8%, P=0.02). Only mild CHF was seen in patients managed by the guidelines. In contrast, of 44 patients with CHF not managed by the guidelines, a majority had moderate to severe CHF. Thus, in patients monitored with serial RNA during D therapy, adherence to these guidelines reduces the incidence and severity of CHF.

EARLY AND LATE EFFECTS OF RIGHT VENTRICULAR INFARCTION ON RIGHT VENTRICULAR SYSTOLIC FUNCTION AT REST AND EXERCISE

Louis J. Dell'Italia, MD, FACC, Richard S. Simmons, MD, Betty Heyl, Ralph Blumhardt, MD, Jack Lancaster, Ph.D., John C. Lasher, MD, Michael H. Crawford, MD, FACC, Robert A. O'Rourke, MD, FACC. The University of Texas Health Science Center, San Antonio, Tx.

It is well appreciated that RV ejection fraction (EF) improves after RV myocardial infarction (MI), but the response of the RV to exercise (ex) after RVMI is unknown. Twenty-one survivors of RVMI had both hemodynamic (both RA pressure (P) ≥10mmHg and RA:pulmonary artery wedge P ratio ≥0.8) and radionuclide angiographic (RNA) (both RVEF <0.40 and akinesis or dyskinesis) criteria of RVMI. In the 6 month follow-up period mean resting RVEF increased from 0.28±0.07[SD] to 0.43±0.08, p<0.01 in 14 pts restudied. To assess latent RV dysfunction and RV functional reserve, respiratory gas exchange and RNA were performed during rapid (1 min stage), upright bicycle ex 1 to 3 yrs after RVMI in 6 pts who had a mean RVEF of 0.28±0.5 at acute MI. At the time of ex, all 6 pts had an FEV_1>85% predicted, stable angina off beta-blocking drugs, and a mean LVEF of 0.56±0.15 (range 0.35 to 0.76). Anaerobic threshold (AT) was determined by a nonlinear increase (↑) in the ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) and a nonlinear ↑ in the $\dot{V}CO_2$. No pt had a low AT on ex. To assure that maximal ex was achieved, all pts exercised 1 min after AT, then for 2 min while peak LV and RVEF were acquired. RVEF ↑ in all pts from 0.48±0.09 to 0.55±0.05 (p<0.05) while LVEF ↑ from 0.56±0.15 to 0.62±0.12 (p=NS) at peak ex. We conclude that pts surviving hemodynmamically important RVMI have no impairment of functional capacity or RV reserve as long as LVEF is not severely depressed and angina is not a limiting factor.

CONTINUOUS MEASUREMENTS OF LEFT VENTRICULAR FUNCTION IN NORMALS AND PATIENTS WITH CORONARY ARTERY DISEASE

Nagara Tamaki, M.D., Tsunehiro Yasuda, M.D., Richard H. Moore, B.S., John B. Gill, M.D., Charles A. Boucher, M.D., F.A.C.C., Herman Gold, M.D., F.A.C.C, H. William Strauss, M.D., F.A.C.C., William T. Tyberg, M.S., Marcia N. Suzuki, Ph.D., Arata Suzuki, Ph.D., Massachusetts General Hospital, Boston, MA and Capintec Inc., Ramsey, NJ

We have developed a device (VEST) for the beat-to-beat measurement of left ventricular (LV) function in ambulatory subjects. To evaluate its clinical applicability, V5 of the ECG and LV function were monitored by the VEST in 5 normals and 5 patients with coronary artery disease (CAD). Following radionuclide ventriculography using the gamma camera, the VEST detectors were affixed over the region of LV. The subject wore the VEST for 2 hours, while performing ordinary activities, such as sitting, walking and exercising. Nuclear and ECG data were recorded on a portable recorder. From the Beat-to-beat LV volume curve, ejection fraction (EF) was calculated. The standard deviation of serial 15 second average EF at rest was less than 3%. The correlation of EF calculated by the VEST and gamma camera was 0.94 at rest and 0.82 during repeated stepwise bicycle exercise. During walking, EF increased by 8-14% in normals, while no significant increase was observed in 2 of the CAD patients. Three ischemic episodes with T wave change were recorded by the VEST. In each episode, EF decreased by 9-12% 60 to 75 seconds before chest pain and increased by 12% within 30 seconds of nitroglycerin. During an episode of ST wave pseudonormalization, EF did not change. During an episode of transient atrial fibrillation, EF decreased by 12%.
We conclude that the VEST is a powerful means for ambulatory monitoring of LV function and ECG simultaneously.

Monday, March 10, 1986
2:00PM–3:30PM, Room #366/367
Alpha and Beta Adrenergic Blocking Drugs

BETA BLOCKER EFFECTS ON CENTRAL NERVOUS SYSTEM. A CONTROLLED COMPARATIVE STUDY.

John B. Kostis, M.D., F.A.C.C., Raymond C. Rosen, Ph.D., UMDNJ-Rutgers Medical School, New Brunswick, New Jersey

Although there are many reports of central nervous system (CNS) effects of beta blockers, controlled comparative studies with objective measures are not available.

In a 16-week double-blind, randomized, placebo-controlled study, atenolol (100mg QD), metoprolol (100mg BID), pindolol (10mg BID), propranolol (80mg BID) and placebo were given to 30 subjects for one week followed by a two week washout period. Objective measures of sleep, sexual function and psychomotor performance were obtained.

Propranolol, metoprolol and pindolol adversely affected sleep (time asleep from 388.5±4.2 min to 375.4±6.1 p< 0.05, number of REM periods 3.78±.16 to 2.67±.15, p <0.001, total REM activity 79.7±6.2 to 58.3±4.91, p<0.001, number of awakenings per night 3.9±.5 to 6.3±.7, p<0.005, nightmares per week 0.0 to 0.21±.09) while atenolol did not appreciably affect these variables.

Pindolol and metoprolol decreased time at maximum penile tumecense (from 21.26±1.88 min to 19.97±2.18 and 17.64±1.87 respectively) as opposed to atenolol (to 27.22±3.08, p<0.05).

Coding vigilance score was depressed by pindolol from 53.5±3.4 to 48.6±3.1, p 0.05 but not affected by metoprolol (54.9±3.1) or atenolol (51.5±3.6). Propranolol effects were generally intermediate between atenolol and pindolol.

Ancillary properties of beta blockers modulate CNS effects: these effects are more pronounced in lipophilic beta blockers and less evident with hydrophilicity. In addition, intrinsic sympathomimetic activity may specifically disrupt REM sleep.

LIPID SOLUBILITY DETERMINES THE RELATIVE CNS EFFECTS OF BETA-BLOCKING AGENTS.

Robert L. Engler, MD, Julia Conant, MD, Al Maisel, MD., David Janowsky, MD, Martin LeWinter, MD. VA Medical Center and University of California San Diego, Departments of Medicine and Psychiatry, San Diego, CA. 92037

The most commonly encountered side effects of B-adrenergic blocking drugs (BBS) are central nervous system (CNS) in origin. Lipophilic BBS concentrate in the CNS and might result in more CNS side effects than hydrophilic BB agents at equal peripheral blocking doses. However, controlled clinical trials have not been made in patients. Accordingly we tested Atenolol (A) (hydrophilic) and Propranolol (P) (lipophilic) in equiblocking doses (peak exercise heart rate reduction) against placebo control (C) using a 6 phase (2 weeks/phase) double blinded crossover design in 17 hypertensive patients. P was given in low (PL, 40 mg bid) and high (PH, 80 mg bid) doses, and A in L (50 mg) and H (100 mg) doses in one of two randomized sequences: C-AL-AH-C-PL-PH, or C-PL-PH-C-AL-AH. At the end of each phase the following were obtained: exercise test, Wechsler Memory Scale (WEM), Profile of Mood States (POMS), Activation/Inhibition Scale (A/I), NIMH behavior rating scale (NIMHB) Beck Depression Inventory and Purdue grooved pegboard test. Of 23 variables examined by repeated measures ANOVA, 5 demonstrated a significant difference between P and A ($p<.05$): A/I, NIMHB, NIMH index of anergy and depression, POMS tension-anxiety, and POMS depression-dejection. Four variables demonstrated trends ($p<.15$): WEM, POMS vigor, POMS anger-hostility, and POMS confusion-bewilderment. In all instances the effect of P was "negative" compared to A indicating a lower sense of well being or poorer short term memory. We conclude that lipophilic properties of BBS contribute to unfavorable CNS side effects in a clinically relevent fashion.

DIFFFERENTIAL EFFECT OF BETA-BLOCKADE ON THE INNERVATED AND DENERVATED HUMAN HEART DURING EXERCISE AND EXOGENOUS CATECHOLAMINE STIMULATION

S. Yusuf [1,2], S. Theodoropoulos[1], N. Dhalla[1], C.J. Mathias[3], J. Wittes[2] and M. Yacoub[1] Harefield Hospital[1], St. Mary's Hospital[3], England and NHLBI[2] Bethesda.

We studied 8 patients with heterotopic cardiac transplantation to evaluate if beta-blockade (BB) has a differential effect on the innervated(IH) or denervated heart(DH) and whether this effect varies during exogenous or endogenous catecholamine(C) stimulation. Heart Rate (HR) increases during incremental isoprenaline infusions(I) and during maximal dynamic exercise on a Bruce Protocol were used to measure responses to exogenous and endogenous C respectively. These studies were repeated before and after propranolol (0.1mg/kg iv). Before BB, during I the DH was more responsive than the IH (+2.27±.34 beats/min/ng of I v +1.59±.26; $p<0.01$) but during peak exercise, the DH and the IH achieved identical HR (147±3 v 149±4 beats/min). Following BB, HR increases to I were similarly attenuated in the DH and the IH, although the DH continued to be more sensitive.(+0.72±.13 +.34±.06) In contrast, during exercise the HR increases were attenuated more in the DH (65±8%) than the IH. (45±9%,$p<0.01$)
Conclusions: The DH is more sensitive to exogenous C than is the IH, probably reflecting an increased density or affinity of beta-receptors. This upregulation appears to be sufficient to increase the HR of the DH to that of the IH during peak exercise. BB attenuates the DH and IH similarly during exogenous C stimulation, but has a more marked effect on the DH during exercise C reflecting the ease by which the IH, with a dual source of sympathetic stimulation, overcomes BB.

COMPARISON OF LABETALOL TO PROPRANOLOL IN PATIENTS WITH BOTH ANGINA PECTORIS AND HYPERTENSION: A DOUBLE-BLIND STUDY.

William Frishman, M.D., F.A.C.C., Shlomo Charlap, M.D., Bruce Kimmel, M.D., Larry Laifer, M.D., Marcia Poland, B.A., William Shapiro, M.D., F.A.C.C., Albert Einstein Medical School, Bronx, N.Y.

In a randomized, placebo(pl)-controlled, parallel design trial, the efficacy and safety of labetalol (L), an α_1-β-adrenergic blocker with direct vasodilatory activity, was compared to that of propranolol (P) in 16 patients with stable angina, an abnormal exercise test, and high BP (standing diastolic BP >90mmHg and <115mmHg). Patients received pl for 4 wks, then either L (100-800mg BID) or P (40-420mg BID) titrated over 4 wks to achieve both angina and BP control, followed by a 4 mos double-blind maintenance phase. Rest and exercise HR and BP, angina frequency, nitroglycerin consumption, and treadmill exercise time (Bruce) were assessed. Angina attacks/wk were reduced from pl, and exercise tolerance increased comparably with both L and P (all $p<0.01$). Nitroglycerin needs were reduced. Standing BP was reduced by both drugs from pl baseline (157.3±23.2/103.1±12.3 to 130.0±15.8/83.0±6.5 with L; 144.0±16.3/96.0±5.9 to 129.1±23.0/87.0±6.0 with P, both $p<0.05$). The increment in BP with exercise observed with pl was blunted by both P and L. Compared to pl, both P and L reduced resting HR ($p<0.03$); exercise HR was lower with P than with L ($p<0.05$). The anti-anginal and BP lowering effects were sustained for 4 mos by both P and L with minimal side effects observed with either drug. Thus, P and L appear to be equally effective and safe in patients with both angina and high BP, and by their actions, relieve angina, improve exercise tolerance, and reduce elevated BP.

HEMODYNAMIC AND ENDOCRINOLOGICAL EFFECTS OF A NEW SELECTIVE α_1-BLOCKING AGENT, TERAZOSIN, IN PATIENTS WITH ESSENTIAL HYPERTENSION: RESULTS OF LONG-TERM TREATMENT

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Terazosin HCl (Ter) is a newly developed α_1-adrenoceptor antagonist with a longer plasma half life than prazosin. Fifteen patients with essential hypertension were treated with Ter (1-4 mg/day) for twelve months.
To assess the mechanism of antihypertensive effect of Ter, the hemodynamic and endocrinological responses to Ter were determined before, three and twelve months after the administration of Ter. Blood pressure reduced significantly within two weeks after Ter and its effect was sustained throughout twelve months. Heart rate was slightly increased during the treatment with Ter.
The hemodynamic studies revealed that total peripheral resistance is significantly decreased and cardiac output (dye dilution) is slightly increased, indicating that antihypertensive effect of Ter is mainly mediated by its vasodilation. Blood volume (^{131}IHSA) and plasma volume were not changed after Ter. Plasma renin activity was not changed after Ter, but plasma aldosterone was decreased in response to Ter. Plasma noradrenaline was increased on the third month, but it was returned to the baseline value before Ter on the twelfth month. Thus, terazosin monotherapy lowered blood pressure throughout one year without drug tolerance including volume expansion and/or accentuation of renin-angiotensin-aldosterone system or sympathetic function.

INTRINSIC SYMPATHOMIMETIC ACTIVITY (ISA) BLUNTS EFFECT OF BETA BLOCKADE ON RENIN AT REST BUT NOT DURING EXERCISE

John B. Kostis, M.D., F.A.C.C., Michael Ruddy, M.D., Robert G. Warner, M.D., Grace Bialy, M.D., Susan D. Krieger, R.N., and Nora Cosgrove, R.N., UMDNJ-Rutgers Medical School, New Brunswick, NJ

In a randomized double-blind crossover study pindolol (PIN 12.78±7.9mg BID) and propranolol (PRO 100±62mg BID) were given to 21 hyperten- sives. Resting heart rates were more depressed ($p<0.0002$) by PRO (from 74±11 to 58±10 $p<0.0001$) than PIN (to 69±9 $p<0.05$) while exercise heart rates were equally affected.

Similarly, plasma renin activity (PRA) was suppressed more ($p<0.02$) by propranolol(from 2.8±1.9 ng/ml.h to 1.2±0.4 $p<0.002$) than pindolol (to 2.0±1.4 $p<0.12$) at rest but not with exercise.

Serum potassium was increased by propranolol and pindolol both at rest (from 4.1±0.4 mEq/L to 4.4±0.4, $p=0.007$ for PRO and to 4.4±0.5, $p=0.05$ for PIN) and with exercise (from 4.3±0.3 to 4.8±0.6, $p=0.003$ for PRO and to 4.7±0.5, $p=0.002$ for PIN). Both drugs were equally effective ($p<0.001$)in lowering systolic and diastolic pressure at rest and exercise.

Conclusions: Beta-1 ISA of pindolol counter-balances the effect of beta blockade on heart rate and renin activity at rest but not during exercise. However, the different effect of beta blockade at rest and exercise is not apparent in regards to blood pressure and serum potassium (mediated by beta-2 receptors).

Monday, March 10, 1986
4:00PM–5:30PM, Room #366/367
Treatment of Angina

INDUCTION OF NITRATE TOLERANCE IN HUMAN HEART FAILURE BY CONTINUOUS INTRAVENOUS INFUSION OF NITROGLYCERIN AND REVERSAL OF TOLERANCE BY N-ACETYLCYSTEINE, A SULFHYDRYL DONOR. Milton Packer MD, FACC, Wai Hung Lee MD, Paul Kessler MD, Norma Medina RN, Madeline Yushak RN. Mt. Sinai Sch of Med, New York, NY

To determine if continuous exposure to nitroglycerin (NTG) induces drug tolerance in man (as it does in vitro), 21 pts with heart failure (CHF) were given NTG intravenously (IV) for 48 hrs. Stroke volume index (SVI, ml/beat/m^2), mean arterial (MAP), LV filling (LVFP) & mean right atrial pressures (MRAP, mm Hg), and systemic vascular resistance (SVR, d-s-c) were measured before (Pre), after 2 hrs of 3.2-6.4 mg/min IV-NTG (NTG-2h), after 48 hrs of continuous IV-NTG at same dose (NTG-48h), & 2 hrs after NTG withdrawal (NTG-W). * = p<.05 vs Pre; † = p<.05, 2h vs 48h

	SVI	MAP	LVFP	MRAP	SVR
Pre-NTG	25.6	80.3	26.8	16.3	1572
NTG-2h	30.0*†	70.5*†	17.1*†	11.2*†	1217*†
NTG-48h	28.0*†	80.2†	24.3*†	14.0*†	1367*†
NTG-W	25.3	82.7	26.6	15.6	1578

Tolerance to NTG's initial effects developed within 48 hrs, as variables returned towards pre-NTG values; only 8/21 pts showed any † in LVFP or SVR after NTG-W. Tolerance was not related to changes in weight or plasma renin activity. Before IV-NTG, all pts responded to oral isosorbide dinitrate (ISDN, 40 mg), but none did so after tolerance was induced to IV-NTG. ISDN response returned within 18-24 h (but not within 2-h) of NTG-W.

In 8 pts who developed tolerance to IV-NTG, the addition of N-acetylcysteine (NAC, 200 mg/kg orally) to IV-NTG produced † in SVI and † in LVFP, MAP, MRAP and SVR (all p<.05), thereby restoring NTG's initial effects. Yet, NAC produced no hemodynamic effects in 7 pts who had not developed tolerance to NTG.

In conclusion, in most pts with CHF, continuous NTG therapy produces the rapid development of organic nitrate tolerance and cross-tolerance, which may result (in part) from the depletion of critical sulfhydryl groups at hypothetical nitrate receptor sites.

EARLY TOLERANCE TO HEMODYNAMIC EFFECTS OF SUSTAINED NITRATE THERAPY WITH HIGH-DOSE TRANSDERMAL NITROGLYCERIN IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE.
Arie Roth, MD, Daniel Kulick, MD, Lee Freidenberger, RN, Robert Hong, MD, Shahbudin H Rahimtoola, MD, FACC, Uri Elkayam, MD, FACC. LAC-USC Medical Center, Los Angeles, CA

Sustained therapy with transdermal nitroglycerin (TNTG) has been shown to result in early development of tolerance in patients(pts) with angina pectoris. In order to establish whether same phenomenon exists in heart failure (CHF), we compared the temporal hemodynamic effect of the 1st & the 2nd dose of TNTG 120mg given q 24hr in 11 pts who had ≥20% reduction in pulmonary artery wedge pressure (PAW). 1st dose TNTG resulted in significant reduction in right atrial pressure (RA), pulmonary artery pressure(PA) & PAW lasting 24hrs: (C=control,*p<.05 vs C)

	C	2hrs	4hrs	8hrs	12hrs	16hrs	20hrs	24hr
RA	10±4	7±4*	6±4*	6±3*	7±4*	8±4*	8±4*	7±4*
PA	38±7	28±7*	27±7*	26±7*	28±7*	32±5*	31±7*	31±6*
PAW	26±6	17±6*	16±6*	15±6*	18±6*	19±4*	20±5*	19±7*

However, a comparison between hemodynamic measurement after 2-6hrs after 1st & 2nd TNTG dose showed:

	1st dose			2nd dose		
	2hr	4hr	6hr	2hr	4hr	6hr
RA	7±4	6±4	6±3	9±5*	8±5**	9±6***
PA	28±7	27±7	27±6	32±8*	32±7**	33±10***
PAW	17±7	16±6	16±7	22±7*	21±8**	19±8***

* p<0.05 vs 2 hr, ** p<0.05 vs 4hr, *** p<0.05 vs 6hr

The effect of the 2nd dose TNTG was significantly attenuated when compared to the effect of the 1st dose. Conclusions: In responders the 1st dose of 120mg TNTG leads to significant & continuous reduction in RA, PAW & PA; however, the 2nd dose given 24hr later is significantly less effective. These findings suggest early tolerance to hemodynamic effects of TNTG in patients with CHF.

CUTANEOUS NITROGLYCERIN PATCHES: EFFECT ON CORONARY ARTERIAL DIAMETER.
Abel E. Moreyra, M.D., F.A.C.C., George J. Saviano, M.D., F.A.C.C., John J. Burns, M.D., F.A.C.C., Joseph Lauricella, M.D., John B. Kostis, M.D., F.A.C.C., UMDNJ-Rutgers Medical School, New Brunswick, NJ.

The use of cutaneous nitroglycerin (NTG) patches has raised great interest and also controversy. We studied the coronary dilator and systemic responses to graded doses of NTG in 25 patients undergoing diagnostic coronary arteriography (CA) after discontinuation of all coronary vasodilators for 48 hours. Fifteen patients received a 51 mg NTG patch 2 to 12 hours before CA (treatment group) and 10 patients did not (control group). High resolution coronary angiograms, using 5" image intensification, were examined in a "blind" fashion before and after administration of cumulative doses of intracoronary (IC) NTG (50 to μ350 g). An electronic caliper was used to measure coronary arterial diameter of proximal left anterior descending artery (LAD) and circumflex artery (Cx) segments. Results:

	LAD DIAMETER INCREASE %			Cx DIAMETER INCREASE %		
	← IC NTG →			← IC NTG →		
	50μg	100μg	200 μg	50μg	100μg	200μg
Control	19±4	21±4	28±8	19±9	25±8	21±6
NTG Patch	10±4	12±3	15±7	3±4	7±4	7±4
	p<0.04	p<0.015	p<0.03	p<0.05	p<0.015	p<0.04

At a cumulative dose of 350 μg NTG mean blood pressure decreased 9±5 mm Hg in the control group and 11±6 in the treatment group (NS). Heart rate increased 4±9 beats/min in the control group and 5±7 in the treatment group (NS). Thus, cutaneous NTG patches cause a blunted coronary dilator response to IC NTG, whereas the systemic response is maintained. The data suggest a marked activation of coronary NTG receptors although selective tolerance to IC nitroglycerin cannot be excluded.

FAILURE OF COMBINATION ANTIANGINAL THERAPY WITH DILTIAZEM AND NITROGLYCERIN: ARE TWO DRUGS BETTER THAN ONE?
Jonathan Abrams, M.D., F.A.C.C., and David Hoekenga, M.D., F.A.C.C., Albuquerque, New Mexico

Diltiazem (DZ) and nitroglycerin (NTG) are vasodilators with differing cellular mechanisms of action. Although both have proven antianginal efficacy, it has not been shown that the use of a calcium channel blocker and a nitrate is better than either single drug alone. We compared the effects of DZ only to DZ with oral NTG in angina patients in a double-blind placebo-controlled trial. 12 subjects with angina pectoris and coronary atherosclerosis were treated with oral DZ, DZ + NTG, or placebo (PLAC) during 3 randomly assigned treatment periods of 2-3 weeks each. Patients were on no other antianginal therapy. After 2 baseline treadmill tests (EXT) to insure reproducible EXT response, patients were randomized to DZ 240 mg/d; DZ/240 mg plus oral NTG to maximal tolerance, mean dose 72 mg/d (range 26-78 mg); or placebo. EXT were performed 2.5 hours after dosing. Results:

TIME TO ANGINA OR FATIGUE (sec)

Therapy	Angina Onset	Total EXT Duration	To 1 mm ST ↓
PLAC/PLAC	349	469	311
DZ/PLAC	413†	538†	409†
DZ/NTG	425†	535†	416†

† p < 0.05 DZ/PLAC vs DZ/NTG = NS

4 EXT were stopped due to fatigue: 2 DZ/PLAC, 2 DZ/NTG, NO PLAC/PLAC. Conclusions: DZ monotherapy is an effective antianginal regimen. Addition of high dose oral NTG does not enhance the anti-ischemic actions of DZ in DZ-responsive patients. Combination antianginal therapy with 2 types of vasodilators appears to offer no benefit to patients who respond to DZ alone.

ADDITIVE EFFECTS OF NITRATES AND CALCIUM ANTAGONISTS

Jean M. Lablanche, M.D., Régis Beuscart, M.D., Gilles Traisnel, M.D., Jean Louis Fourrier, M.D., Michel E. Bertrand, M.D., F.A.C.C. - Hopital Cardiologique - Lille - France

Nitrates and calcium antagonists may have additive effects with respect to their different cellular mechanisms. Therefore, we designed the following protocol in 12 patients (pts) with variant angina. All had ergometrine provoked coronary spasm during coronary arteriography. Within a period of 3 days, they received either 20 mg of 5 ISMN, (5 isosorbide mononitrate) or nifedipine (10 mg) and finally a combination of the 2 drugs. An ergometrine test with incremental doses (0.05, 0.10, 0.20, 0.40 mg) was performed at the same hour of each phase and 60 minutes after the drug administration. No pt had a positive test (T+) before the 0.2 mg injection.

	T(-)	T(+)0.4mg	T(-)0.2mg
5 ISMN	3	4	5
Nifedipine	6	4	2
Nif + 5ISMN	10	2	0

By comparison with 5ISMN, nifedipine was superior in 6 pts but inferior in 2 (NS). The combination of nifedipine and 5 ISMN was superior to nifedipine alone in all the 6 patients with a positive test ($p = 0.03$) and superior to 5 ISMN in all except one ($p = 0.01$). These results support the hypothesis that nifedipine and nitrates may have additive effects and their combination is superior to one of these drugs alone in the prevention of coronary arterial spasm.

PROBLEMS OF ANTI-ISCHEMIC DRUG THERAPY IN PATIENTS WITH INSUFFICIENT NITRATE-RESPONSE.

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The oral administration of isosorbide-dinitrate (ISDN) usually leads to a remarkable improvement of exercise(ex)-induced ischemia. There are, however, patients who do not benefit from nitrate therapy,although preload reduction could also be demonstrated in this group of pats. To assess, whether this special group of pats improves after a further increase of myocardial blood-supply with a calcium-antagonist or from a reduction of contractility with beta-blockade we performed a randomized, double-blind and cross over study in 26 consecutive pats with no (n=19) or minor (n=7) response to orally given 80mg ISDN. 3x120mg Verapamil(VERA)as well as 2x80mg propranolol(PROP) were additionally administered for 3 weeks each, followed by another 3 weeks of a single-blind triple therapy. Ex-tests were performed 2 hrs after the morning-ingestions respectively. Pats with standard criteria for CAD were included only if the ST-segment during ex was $\geq$1mm and left-ventricular ejection fraction (EF) at rest was $\geq$ 35%, as determined by radionuclide-ventriculography. Results: (mean $\pm$ one SD)

	CONTROL:	ISDN:	ISDN+VERA:	ISDN+PROP:	TRIPLE:
ST (mm)	2.6±1.1	2.1±1.2	0.9±0.9	0.9±0.7	0.2±0.4
EF-ex(%)	53±11	59±14	59±10	60±10	56±10

Conclusions:

1,Ex-induced ischemia in pats with insufficient nitrate-response can be significantly improved by VERA as well as by PROP.

2, Since VERA and PROP were equally effective, the reduction of contractility seems to be the prevailing mechanism for a successive anti-ischemic therapy in this special subset of pats.

3, Pats with insufficient nitrate-response usually need a triple therapy for optimal anti-ischemic treatment. This can be achieved even without a significant deterioration of EF during ex.

Monday, March 10, 1986
2:00PM-3:30PM, Room #364/365
Pathophysiology of Mitral Valve Disease

INCREASED PLATELET RELEASE PRODUCTS AND AGGREGATION IN SYMPTOMATIC MITRAL VALVE PROLAPSE (MVP)

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Ten symptomatic patients with documented mitral valve prolapse (M and 2D-ECHO) and a stable hyperadrenergic state underwent platelet studies. There were 7 females and 3 males, mean age was 53.2±2.7 years. Values obtained previously in ten normal subjects (sex-matched) were used as reference. Plasma catecholamines were measured by the technique of Peuler and Johnson in the supine (S) position and 10 minutes after assuming a standing (ST) position. The platelet-aggregate ratio (AGR), platelet factor 4 (PF_4), β-thromboglobulin (BTG), thromboxane B_2 (T_xB_2) and Fibrinopeptide A (FPA) were measured. Platelet aggregation to various concentrations (0.23 to 0.91 µg/ml) of ADP, epinephrine and collagen, and to thrombin (0.137, 0.182 U/ml) was tested on PRP. Plasma norepinephrine and epinephrine were significantly elevated in the S (323±29 pg/ml vs control 201±10 pg/ml, p<.001) as well as in the ST position (747±79 vs 411±20 pg/ml, p<.001). Free epinephrine and dopamine were normal in S and ST positions

	BTG	PF_4	T_xB_2	AGR
pts (x±SEM)	36.6±5.2	16.3±5.6	456±48	.72±.04
Controls	21.3±1.8	2.3±0.7	386±26	.95±.03
p value	<0.01	<0.02	<NS	<0.001

The ratio of platelet aggregates in blood and the levels of BTG and PF_4 were increased in all patients as compared to controls (p<0.01). Ex vivo platelet aggregation was increased by more than 45% (p<0.05) above control values to ADP, collagen and thrombin but was found normal to epinephrine in most patients. One patient presented spontaneous platelet aggregation.

We conclude that in addition to platelet hyperaggregability which appear related to the increased hyperadrenergic state, platelet activation is taking place in patients with MVP and may reflect the increased thromboembolic risk in these patients.

Ia ANTIGENS ON VALVULAR TISSUE FROM PATIENTS WITH ACTIVE RHEUMATIC CARDITIS.

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Class II major histocompatibility complex (MHC) antigens play an important role in activating and directing the immune response. If this system is triggered to respond to the host's own tissue, eg. valvular fibroblasts, destructive immune phenomena may occur. Acute rheumatic fever with carditis and hemodynamically severe valvular insufficiency was diagnosed in 12 black pts, according to the modified Jones criteria. There were 7 males and 5 females with a mean age of 12 yrs (range 9-16). All were in NYHA Class III (8 pts) or IV, and underwent mitral (9 pts) or double valve surgery. The presence of active valvulitis was confirmed macroscopically at operation and histologically on subsequent light microscopy. Valvular tissue was examined for the presence of Ia antigens employing both fluorescent and peroxidase staining techniques. Surface Ia antigen expression was demonstrated on fibroblasts within the heart valves of all pts, using the Ortho-mune OKIa monoclonal antibody. This was confirmed with anti-Ia New England Nuclear antibody. Control heart valve tissue from pts dying with other cardiac pathologies or following trauma showed no evidence of autoimmune activity. The aberrant expression of the Ia antigen (MHC Class II) on heart valve fibroblasts during active rheumatic carditis may have an important role in the development of this disease.

PREVALENCE AND SEVERITY OF MITRAL REGURGITATION IN THE MITRAL VALVE PROLAPSE SYNDROME: A DOPPLER ECHOCARDIOGRAPHIC STUDY OF 80 PATIENTS

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To define the exact prevalence and severity of mitral regurgitation (MR) in patients (pts) with mitral valve prolapse (MVP), Doppler echocardiography (echo) was performed in 80 consecutive pts (22 men, 58 women), aged 38±16 years, who had MVP diagnosed by two-dimensional (2D) echo. Of the 80 pts, 16 (20%) were asymptomatic and 11 (14%) had a normal physical examination (no click or murmur). The M-mode echo was negative for MVP in 11 (14%) pts and equivocal or non-diagnostic in 19 (24%) pts. On 2D-echo, prolapse of the anterior mitral leaflet was evident in 45 (56%) pts, while both leaflets were involved in 35 pts. Mitral regurgitation was evaluated using the pulsed mode Doppler and was quantified by the mapping technique as minimal or mild when a holosystolic regurgitant jet was recorded just above the mitral valve into the left atrium (LA), and as moderate or severe when the jet was detected up to mid- or distal LA. Mitral regurgitation was found in 55 of 80 (69%) pts and it was minimal or mild in 47 (59%) and moderate or severe in 8 (10%) pts. In 20 of the 55 (36%) pts with MR by Doppler, a systolic murmur was not detected and all of them had mild MR. Left atrial and left ventricular size on M-mode echo were significantly smaller in pts with mild or no MR as compared to the 8 pts with moderate or severe MR. All these 8 pts were men (6 over 50 years) and they usually presented with dyspnea and a holosystolic murmur; the MVP was holosystolic by M-mode and involved both leaflets by 2D-echo. Two of the 8 pts required mitral valve replacement. In the remaining pts, the type of MVP by M-mode (holosystolic or late systolic) and the number of mitral leaflets involved by 2D-echo (anterior only or both) were not predictive of the presence or absence of MR.

In conclusion: 1) MR as assessed by Doppler is common in pts with MVP, but is usually mild and may not be associated with an audible murmur. 2) In our series, significant MR was rare (10%) and usually occurred in men with MVP, who were over 50 years old.

MITRAL VALVE PROLAPSE-SUDDEN DEATH WITH LONG TERM SURVIVAL

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Sudden death occurring in patients (pts) with mitral valve prolpase (MVP) has been reported, the natural course of MVP pts who survived cardiopulmonary resuscitation (CPR) has not. Of 9 pts (7 female and 2 male, age 22-66, mean 33) with MVP and sudden death, 7 out-of-hospital, 2 in-hospital) ventricular fibrillation was documented in 8 and CPR was successful in 7. Prior to sudden death 8 pts had palpitations, 3 syncope and 1 no symptoms. Click- murmur was present in 7 and click only in 2. In the 7 survivors cardiac catheterization showed MVP and normal coronary arteries in all: echocardiogram showed MVP in all. One pt had prolonged electrical systole (QT). Electrophysiologic studies in 7 pts showed nonsustained ventricular tachycardia (<10 beats) in 2, mild sinus node and atrioventricular node disease in 2, intra-His block in 1 and no abnormalities in 2. The 7 CPR survivors (still alive) are followed from 1 to 15 years (mean 5.2); during the follow-up period 2 pts had palpitations, 1 orthostatic hypotension and near syncope, 1 palpitations plus dyspnea and 3 no symptoms. Three pts were treated with β-blocking drugs, 2 with β-blocking drugs plus class I antiarrhythmics, 1 with a pacemaker plus antiarrhythmics, and 1 with valve replacement, pacemaker and antiarrhythmics. The present study confirms previous reports that a subset of MVP pts with long history of palpitations-arrhythmias and syncope may be prone to sudden death. In addition this study defines the natural course of MVP-sudden death pts after successful CPR. The long term prognosis in this group of pts appears better than that of other causes of sudden cardiac death.

EARLY DIASTOLIC FILLING DYNAMICS DURING EXPERIMENTAL MITRAL REGURGITATION IN THE CONSCIOUS DOG

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To study the diastolic mechanisms of left ventricular adaptation to acute volume overload in mitral regurgitation (MR), 5 dogs were instrumented with a micromanometer (LV pressure) and sonomicrometers (wall thickness, long and short axes). LV volume, circumferential wall stress and eccentricity of LV chamber (derived from the values of long and short axes) were calculated throughout diastole. Measurements were made at control(C) and up to 4 weeks after creation of MR. Heart rate, peak systolic wall stress and peak(+)dP/dt showed no significant changes. At 4 weeks after MR end-diastolic volume increased (C=79±4, MR=119±9 ml, $p<0.001$). Peak filling rate (C=385±50, MR=902 ±172 ml/sec, $p<0.002$) and filling fraction during first 40% of diastolic time (FF40) (C=51±1, MR=76±5%, $p<0.001$) increased with no significant change of diastolic time intervals. Over the period of adaptation to the volume overload, FF40 correlated with end-diastolic volume ($r=0.52$, $p<0.02$) and total stroke volume ($r=0.80$, $p<0.001$). Eccentricity at end-systole decreased (C=0.81±0.02, MR=0.79±0.03, $p<0.05$) and reduction of this ratio during first 40% of diastolic time was greater in MR than in C (C=0.05±0.01, MR=0.11±0.02, $p<0.005$). We conclude that the LV accommodates the need for increased diastolic volume during acute MR by increasing proportionately the filling and spherical deformation during the first 40% of diastole.

LACK OF ASSOCIATION OF CARDIAC SYMPTOMS WITH MITRAL VALVE PROLAPSE IN SIXTH GRADE SCHOOLCHILDREN.

Cynthia L. Arfken, Ph.D., Anthony S. Lachman, M.D., F.A.C.C., Peter Schulman, M.D., F.A.C.C., Grover C.M. Farrish, M.D., Diane S. Slowik, and Margaret J. McLaren, M.D., Yale University, New Haven and University of Connecticut, Farmington.

Prior studies linking chest pain and other cardiac symptoms to mitral valve prolapse may be biased by methods of recruitment in that the presence of disease calls attention to symptoms. To avoid this potential bias, 591 non-care-seeking children, ages 9-14, 31 with auscultatory mitral valve prolapse, which at that time was unknown to them, completed a structured questionnaire wherein potential cardiac symptoms were elicited. Chest pain or discomfort anytime in life was reported in 62% of children without mitral prolapse and in 42% of those with this condition ($P<.05$). Fatigue, palpitations, dizziness and fainting were more common in the non-prolapse group (NS). Only dyspnea on running up one flight of stairs was slightly more common in the children with prolapse (NS). Overall, 26% of the non-prolapse group and 45% of the prolapse group reported no symptoms ($P<.05$). Among children reporting symptoms, those with mitral prolapse reported no more symptoms than those without: 1.6 vs. 1.5, (NS). Findings did not differ between genders. Thus, cardiac symptoms were more common in adolescents without mitral valve prolapse than in those with this condition when symptoms were elicited when subjects were unaware of their condition. These results fail to support the contention that chest pain and other cardiac symptoms are more common in persons with mitral valve prolapse.

Monday, March 10, 1986
4:00PM-5:30PM, Room #364/365
Echo Doppler Methods for Assessment of Valvular Heart Disease

DOPPLER OVERESTIMATION OF SYSTOLIC AORTIC VALVE GRADIENT IN PATIENTS WITH AORTIC REGURGITATION.

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Aortic transvalvular pressure gradients have been estimated using Doppler ultrasound in pts with aortic stenosis. We compared the accuracy of calculation of aortic transvalvular pressure gradients (ΔP) obtained using continuous wave Doppler (CWD) ultrasound velocities with measurements obtained from direct pressure recordings in pts with severe aortic regurgitation (AR).

CWD studies were performed within 24 hrs of cardiac catheterization on 14 pts with severe (3-4+) AR & absent to moderate aortic stenosis. CWD measurements of the aortic valvular flow peak velocity allowed calculation of the transvalvular ΔP by using the modified Bernoulli equation ($\Delta P = 4V^2$).

RESULTS: Mean heart rate was comparable for CWD and pressure recordings ($p>.2$). Direct pressure recordings using a fluid-filled catheter showed peak to peak aortic ΔP ranging from 0 to 35 mm Hg. Mean ΔP was 30 ± 16 mm Hg by CWD and 13 ± 12 mm Hg by direct pressure recordings ($p<.001$). Comparison with CWD ΔP showed overestimation of ΔP by CWD ranging from 1 to 49mm Hg (mean 17), $r=.72$, SEE=8.4 mm Hg.

We conclude that CWD cannot reliably predict systolic aortic pressure gradients when severe AR is present.

NORMAL LEFT VENTRICULAR ECHOCARDIOGRAMS IN PATIENTS WITH AORTIC STENOSIS

Mark Lipton, M.D., James Slater, M.D., Paul Kramer, M.D., William Schwartz, M.D., Howard Winer, M.D., F.A.C.C., Itzhak Kronzon, M.D., F.A.C.C., Ephraim Glassman, M.D., F.A.C.C. New York University Medical Center, New York, NY

Patients with significant aortic stenosis occasionally demonstrate normal LV wall thickness on echocardiography (echo). In order to assess the implication of a normal LV echo in aortic stenosis, the hemodynamic, echo and clinical data of 78 patients who underwent cardiac catheterization and were found to have aortic stenosis without other significant valvular disease were analyzed. 17/78 (21%) of these patients had normal LV wall thickness and end-diastolic internal dimension. LV wall motion scores and coronary scores were derived by analysis of the angiograms.

	normal LV echo	abnormal LV echo	
Mean Gradient	59.9±9.6(SEM)	56.2±3.2	NS
Aortic Valve Area	0.82±0.15	0.76±0.04	NS
LV Systolic Pressure	202±6	200±4	NS
LVEDP	18.8±1.7	21.8±1.0	NS
Cardiac Index	3.07±0.91	2.82±0.07	NS
Coronary Score	3.47±0.90	4.07±0.52	NS
Wall Motion Score	2.50±1.49	4.20±0.91	NS
Age	65.2±2.3	70.0±1.26	NS

There were no significant intergroup differences in symptoms or in the prevelance of ECG evidence of LV hypertrophy. We conclude that patients with clinically important aortic stenosis frequently (21%) do not present with LV hypertrophy or dilatation on echo. Furthermore, the normal LV echo patients do not differ from the abnormal LV echo patients in their symptoms or cardiac catheterization data.

DIAGOSIS AND QUANTIFICATION OF AORTIC REGURGITATION WITH PULSED DOPPLER ECHOCARDIOGRAPHY IN COMBINED VALVULAR DISEASE.

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To test the ability of pulsed doppler echocardiography (PDE) in detection and quantification of aortic regurgitation (AR),64 consecutive patients (14-74 years) with aortic and mitral valve disease were examined clinically and by echocardiography before cardiac catheterization. The severity of AR was determined angiographically (I-IV) and compared to the extent of the regurgitant jet in the left ventricle measured by PDE.

In 15 of 64 patients (2 mitral stenosis,5 mitral insufficiencies,3 combined mitral lesions,4 aortic stenosis,1 combined aortic and mitral lesion) neither angiography nor PDE showed AR (specificity 100%). Apart from 3 patients with poor echo quality PDE correctly detected AR in 46 of 49 patients (sensitivity 94%).Sensitivity of the clinical examination was 61% and m-mode sensitivity 57%.The PDE degree of AR correlated strongly with angiography (r= 0.91).In 4 of 5 patients with severe aortic stenosis the AR I was slightly overestimated.Differentiation between AR III and IV by PDE was not possible. Mitral valve disease did not affect quantification of AR (n=34 patients).

Conclusion:Pulsed doppler echocardiography is superior to auscultation and echocardiography in detecting aortic regurgitation in the presence of mitral valve disease and is reliable in estimating the degree of aortic regurgitation.In patients with severe aortic stenosis AR I is slightly overestimated by PDE.

INACCURACY OF PULSED DOPPLER TECHNIQUE IN ESTIMATING MEAN PULMONARY ARTERY AND PULMONARY WEDGE PRESSURE IN AN UNSELECTED PATIENT POPULATION.

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To assess the accuracy of pulsed Doppler(D)technique in measuring mean PA pressure(PAP) & PA wedge pressure(PWP)& their changes after intervention in an unselected patient population,we obtained simultaneous D & fluid-filled catheter(C) measurements(meas) in 34 consecutive patients (pts) during routine cardiac catheterization. 26 pts had technically satisfactory studies. A 1st set of meas was obtained before performing an LV angiogram & a 2nd soon after injection of contrast dye. Pressure & D meas were independently analyzed by 2 blinded observers. Mean D PAP & PWP were derived from acceleration time(AT) & calculated using previously published regression equations: PAP=-.45xAT+79, PWP= 57-.39xAT. Mean PAP meas by C ranged from 13 to 46mmHg, mean 25.9±7.7(m±SD) & mean PWP ranged from 6 to 45mmHg (mean 18.6±7.7). When measured by C, the intervention effectively changed mean PAP & PWP by 22%, $p<.05$,& 22%, $p<.05$, respectively; however, D failed to detect such changes(3%,$p>.05$ & -20%,$p>.05$, respectively). Analysis of PAP values before & after intervention showed a poor correlation between C & D ($R=.48$, SEE =6.62,& $P<.001$). Similar poor correlation was found when PWP was analyzed($R=.49$,SEE=6.1,$p<.001$). In detecting mean PAP values of >22mmHg,D had a sensitivity of 64%,specificity of 28.5%,accuracy of 60%. In detecting mean PWP values >12mmHg,D had a sensitivity of 94%, a specificity of 50%, accuracy of 77%. We conclude: 1) In an unselected patient population,D meas of mean PAP & PWP are inaccurate; 2) mean PAP & PWP meas by D are unreliable in detecting hemodynamic changes after intervention.

LEFT ATRIAL SPONTANEOUS ECHO CONTRAST IN MITRAL VALVE DISEASE - AN INDICATOR OF INCREASED THROMBEMBOLIC RISK

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Left ventricular (LV) spontaneous echo contrast (SEC) is a well-known phenomenon in patients (pts) with seriously impaired LV function. In the left atrium (LA), however, SEC is only occasionally noted. We studied 38 pts with mitral stenosis (MS; group I) and 31 pts after mitral valve replacement (MVR; group II) using conventional transthoracic (C) and transesophageal (TE) 2D-echocardiography (ECHO). Twenty-nine group I pts and 25 group II pts had atrial fibrillation (AF).

Results: SEC was not seen on any C-ECHO but could clearly be identified by TE-ECHO in 27 group I pts (71 %) (22 with AF) and 15 group II pts (48 %) (all with AF). Pts with SEC had larger LA diameters than those without (group I: 61.4 ± 27.0 mm vs 50.3 ± 11.0 mm; group II: 70.3 ± 15.0 mm vs 50.8 ± 16.0 mm; $p < 0.001$). Fourteen of the 42 pts with SEC had history of arterial embolism (EMB) and 6 had LA thrombi (TH) proven by surgery and/or ECHO; 18 SEC-pts (43 %) had EMB and/or TH. In contrast, only 1 of the 27 pts without SEC (4 %) had EMB, and no pt had TH ($p < 0.005$).

Conclusion: LA-SEC in pts with MS both before and after MVR can easily be detected by TE-ECHO; SEC is in particular found in pts with large LA and may be considered an indicator of an increased thrombembolic risk requiring consequent anticoagulant therapy.

INTRAOPERATIVE DECISION MAKING IN TRICUSPID VALVE SURGERY BY 2-D ECHO. Martin E. Goldman, M.D., F.A.C.C., Bruce P. Mindich, M.D., F.A.C.C., Theresa Guarino, R.N., Valentin Fuster, M.D., F.A.C.C.. Mt. Sinai Hospital & St. Luke's-Roosevelt Hospital Center, NY, NY.

Secondary tricuspid (T) regurgitation (R) is due to RV dilatation in response to PA hypertension from left sided heart (LH) disease. While TR may partially resolve following repair of the LH lesion, significant residual TR may increase postoperative morbidity. To quantify the severity of TR and to determine if T repair was necessary, 2-D contrast echo (2DCE) was performed in 50 patients (pts) intraoperatively . In pts with TR, injection of D5W into the RV generated echogenic contrast with systolic reflux of contrast into the RA, scored as 0 to 4+. Systolic PA pressure (mmHg), 2DCE pre and post LH procedure and baseline T annulus (TVA) dimension (mm) were also measured. Pts were divided by severity of intraoperative 2DCE TR: 0-2+ TR and 3-4+ TR. (* = $p<0.0001$,** = $p<0.01$)

TR	n	Pre-PA	Post-PA	TVA
0-2+	36	31 ± 13	27 ± 10	26 ± 3
3-4+	14	44 ± 13*	35 ± 8**	38 ± 4*

TVA correlated better with TR severity ($r=0.75$, $p<0.0001$), than pre-PA ($r=.48$, $p<0.02$). All 14 pts with TVA ≥ 30 mm had 3-4+ TR. Importantly, the 9/14 pts with initial 3-4+ TR with severe persistent TR post LH operation, who required T repair could be identified only by 2DCE, but not by hemodynamics nor palpation. Therefore, large TVA may indicate chronic RV dilatation and dysfunction which may remain despite a reduction in PA pressure. Intraoperative 2DCE can identify those pts (TVA ≥30 & 3-4+ TR) who will have residual 3-4+ TR and may have significant benefit from TV repair.

Monday, March 10, 1986
2:00PM–3:30PM, Room #157
Coronary Artery Surgery—I

FIFTEEN HUNDRED CORONARY REOPERATIONS: RESULTS AND DETERMINANTS OF EARLY AND LATE SURVIVAL

Bruce W. Lytle, MD, FACC, Floyd D. Loop, MD, FACC, Delos M. Cosgrove, MD, FACC, Paul C. Taylor, MD, Marlene Goormastic, MPH, Carl C. Gill, MD, FACC, Leonard A.R. Golding, MD, FACC, Robert W. Stewart, MD,
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Fifteen hundred consecutive patients undergoing a first reoperation for coronary revascularization were reviewed to determine early and late results and predictors of survival. To examine trends, patients were subdivided into cohorts based on the year of operation: Group A (1967-78, 436 patients), Group B (1979-81, 439 patients), and Group C (1982-84, 625 patients). Overall operative mortality was 3.3% (50 deaths); 4.6%, 2.3% and 3.2% for Groups A, B and C, respectively. Comparison of cohorts showed that Group C had increased numbers of women and patients with triple-vessel disease, left main stenosis (≥50%), abnormal left ventricular function, age ≥70 yrs.,and graft failure as a surgical indication (all $p<0.001$). The mean interval between operations increased from 50 mos. for Group A to 84 mos. for Group C. At reoperation, Group C patients received more grafts, more mammary artery grafts and had a higher prevalence of complete revascularization (all $p<0.001$). Univariate and multivariate analyses identified left main stenosis ($p<0.0001$), Class III or IV symptoms ($p=0.0002$), advanced age ($p=0.0004$), Group A ($p=0.005$) and diabetes ($p=0.05$) as predictors of increased in-hospital mortality. Abnormal left ventricular function (LVF) was associated with increased risk for Group A ($p=0.05$) but not for Group B or C. Follow-up (mean interval 68 mos., range 14-171 mos.) of the first 1000 patients (excluding 30 who died in hospital) documented 5-yr. survival of 90%. Multivariate testing identified advanced age ($p<0.0001$), abnormal LVF ($p=0.005$) and triple-vessel disease ($p=0.03$) as predictors of decreased late survival.

CORONARY ARTERY BYPASS GRAFT SURGERY FOR THE THIRD TIME OR MORE. THE RESULTS OF 90 CONSECUTIVE OPERATIONS.

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During the last 11 years, 87 patients (PTS) underwent 90 consecutive coronary artery bypass graft (CABG) surgeries performed for the third time or more. Clinical characteristics showed that 67 PTS (77%) were men, the mean age was 54 years (range: 28-72). Eighty PTS (89%) had triple vessel disease, 51 PTS (57%) had a prior myocardial infarction, and 32 PTS (36%) had a left ventricular ejection fraction ≤ 50%. All PTS had angina preoperatively with 88/90 PTS (CASES) (98%) having Class III-IV angina. Eighty PTS had 2, 9 PTS had 3, and 1 PT had 4 prior surgeries. Direct myocardial revascularization was performed in all PTS with a mean of 3.2 grafts (range: 1-6) placed. Additional procedures included Vineberg implants on 4 PTS (4%), left ventricular aneurysmectomy on 4 PTS (4%), and coronary artery endarterectomy on 32 PTS (36%). Complications encountered included 8 hospital deaths (9%) and 4 nonfatal perioperative myocardial infarctions (4%). At hospital discharge, 76/79 surviving PTS (96%) were symptomatically improved. Followup data (excluding 5 foreign PTS) for a period of 4-132 months (mean: 34 months) is available on 74/75 PTS (98%). Clinical evaluation showed 33 PTS (48%) were asymptomatic; the remaining 36 PTS (52%) were symptomatic: 36 PTS (52%) with angina (25, Class II; 10, Class III; 1, Class IV). There were 5 late deaths occurring between 1 and 90 months. Three PTS underwent repeat CABG surgery at 7, 54 and 55 months postoperatively. These data demonstrate that repeat CABG can be accomplished in severely symptomatic PTS (regardless of the number of prior surgical procedures) with gratifying operative success and long-term clinical results.

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COMPARISON OF INTERNAL MAMMARY ARTERY AND SAPHENOUS VEIN GRAFTS USING STRESS THALLIUM SCINTIGRAPHY.

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Several studies have documented superior long term patency of the internal mammary artery (IMA) compared to the saphenous vein (SV) as a conduit in coronary surgery. To determine adequacy of flow, we performed stress thallium scintigraphy in 130 patients 4-6 weeks following coronary reconstruction. There were 143 IMA and 237 SV grafts.

A standard or modified Bruce protocol was used.Patients were exercised to 80% of predicted heart rate or until limiting factors occurred. Thallium scintigrams were reviewed by 2 independent radiologists. Ischemia was demonstrated by perfusion deficits at peak stress which were absent in the 2-hour delayed film. Defined areas were anterior septal, lateral, and postero-inferior.

Ischemia was documented in 18.2% (26/143) of areas supplied by IMA grafts, compared to 7.6% (18/237) of regions revascularized by SV conduits. This was statistically significant (P=0.05).Anterior wall ischemia was noted in 22% (21/96) of IMA compared to 5% (1/20) of SV grafts. Although this was not statistically significant, a definite trend is suggested.

This study suggests that ischemia demonstrated by stress thallium scintigraphy in the early post-operative period is more common with the IMA than the SV graft. This may reflect graft occlusion or inadequate flow in a patent graft during exercise.

CAN THE HIGH RISK UNSTABLE ANGINA PATIENT BE IDENTIFIED? VA Cooperative Study #28. Prepared by G.V.R.K. Sharma, M.D., R. Deupree, Ph.D., H. Olson, M.D., N. Shadoff, M.D., S. Scott, M.D., R. Luchi, M.D., S.F. Khuri, M.D., A.F. Parisi, M.D. West Roxbury VAMC, Harvard Medical School, Boston and the Coordinating Center, West Haven, CT.

To identify the high-risk patients (pts) with unstable angina (UA) and evaluate their response to treatment, 468 pts were randomized to medical therapy (M), or coronary bypass surgery (S) in a multicenter, prospective study. Pts with left main coronary disease were excluded. Based on clinical presentation pts were stratified into Type I or Type II: those with accelerated exertional angina (IA); rest angina complicating exertional angina (IB); severe, recent onset angina (IC); prolonged (>15') rest angina with ST↓ or T↓ on EKG (II). The strata were identical when clinical (age, sex, risk factor) and angiographic profiles (number of vessels involved, left ventricular function (LVF)) were compared. Mortality rates at 2 yrs:

Type	Mortality		
	M%	S%	P=
IA	7.3(4/55)	6.1(3/49)	0.82
IB	7.1(7/98)	8.5(7/82)	0.73
IC	13.5(5/37)	5.7(3/53)	0.19
II	12.8(6/47)	6.4(3/47)	0.29
IC+II	13.1(11/84)	6.0(6/100)	0.15
IC+II (2 or 3 vessel CAD)	15.6(10/64)	5.4(4/74)	0.05*
IC+II (abnormal LVF)	15.0(3/20)	0.0(0/30)	0.03*

While the mortality was not different between M and S in IA and IB, a trend towards improved mortality was seen in IC and II. The results with surgery were significantly (*) better when IC and II were combined and subgroups of pts with multivessel CAD and abnormal LVF analyzed. Conclusion: UA pts with severe recent onset angina or those with prolonged rest angina with ST↓ or T↓ on EKG appear to have higher risk with M and should benefit from early S.

A PROSPECTIVE EVALUATION OF POSTOPERATIVE FLOW RESERVE IN INTERNAL MAMMARY ARTERY BYPASS GRAFTS.

Alan M. Johnson, M.D., Denny D. Watson, Ph.D., Robert S. Gibson, M.D., F.A.C.C., and Irving L. Kron, M.D., F.A.C.C. Univ. of Virginia Med. Ctr., Charlottesville, Virginia.

The internal mammary artery (IMA) has been advocated for use in bypass grafting due to its superior long term patency when compared to saphenous vein. Concern exists that flow through the IMA may be inadequate during periods of peak myocardial demand. To investigate this, 24 consecutive patients with a mean proximal LAD stenosis of 87.5% were selected for coronary bypass using the IMA. Within 8 weeks of surgery, all underwent evaluation with exercise Thallium-201 (TL-201) scintigraphy. A mean maximum predicted heart rate of 101% and rate pressure product of 29.9 X 10^3 were achieved at a mean workload of 8.1 METS. TL-201 activity, expressed as a ratio of anteroseptal activity to posterolateral wall activity (or inferior wall activity if the posterolateral wall was deemed abnormal) was 0.97 $\pm$ 0.15. A second group of 25 patients determined to be normal by either normal ventriculography and coronary angiography (16) or by a normal history, physical exam, graded exercise treadmill test, and myocardial distribution of TL-201 (9), was similarly evaluated. This group reached a mean maximum predicted heart rate of 85.3% and a mean rate pressure product of 23.7 X 10^3, at a mean workload of 9.6 METS. The mean septal to posterolateral wall TL-201 activity ratio for these normal patients was 1.0 $\pm$ 0.15. No significant difference in relative post-exercise anteroseptal TL-201 activity between normal patients and IMA bypass recipients can be demonstrated. The internal mammary artery provides adequate coronary flow at peak myocardial demand.

REOPERATION FOR CORONARY ARTERY DISEASE.

Robert J. Hall, M.D., F.A.C.C., MacArthur A. Elayda, M.D., Albert G. Gray, Ph.D, Denton A. Cooley, M.D., F.A.C.C., Clayton Foundation for Research-St. Luke's Episcopal Hospital, and Texas Heart Institute, Houston, Texas.

To determine the operative mortality and long term results in pts undergoing coronary artery bypass reoperation (CABR) for recurrent angina pectoris, we reviewed the results of our institutions' 15 yrs experience. There were 1607 pts who underwent CABR from 1970-84. Of these, 958 had their initial CAB (CABI) and CABR in our institution; 649 had their CABI elsewhere. Only the results of 958 pts are included in this study. Three angiographic indication groups were identified; 1) graft failure (GF), 17%; 2) progression of coronary atherosclerosis (PCA), 34%; and 3) combination of GF and PCA, 49%. Grafts per pt increased from 1.9 per pt at CABI to 2.7 at CABR. Bypasses performed were single in 117 (12.2%); double, 345 (36.0%); triple, 365 (38.1%); quadruple or more in 131 (13.7%). Early mortality (EM) was 9.2% (88/958). This was higher compared to the 2.8% (860/30,464) of the total institutions experience on pts undergoing CAB alone for the same time period. Major causes of EM were cardiac in origin in 80% and non-cardiac in 20%. EM for men was 8.7% (74/847) and 12.6% (14/111) in women. EM according to age, except for men in the 5th decade and women in the 6th decade, increased progressively with age. 57% of pts had history of MI before CABI while 145 had MI prior to CABR. At follow-up, angina was relieved or improved in 75%. Actuarial survival revealed a 5 yr survival (YS) of 80% or an average annual attrition rate of 4% and a 10 YS of 58% or an annual attrition of 4.2%. These survival rates are low compared to the 5 and 10 YS of 90% and 73% noted in our total institution CAB pts. These data revealed that CABR has a higher EM compared to those pts undergoing CAB for the first time, and good long term symptomatic relief and long term survival can be achieved by CABR in pts who have recurrent angina after CABI despite the higher risks involved at CABR.

Monday, March 10, 1986
4:00PM–5:30PM, Room #157
Coronary Artery Surgery—II

IMPROVED SURVIVAL WITH CORONARY BYPASS SURGERY IN PATIENTS WITH SEVERE CORONARY ARTERY DISEASE: A MATCHED CASE CONTROL STUDY IN PATIENTS WITH POTENTIALLY OPERABLE DISEASE Gary J Vigilante, MD; William S Weintraub, MD, FACC; Lloyd W Klein, MD, FACC; Ricky M Schneider, MD, FACC; Paul A Seelaus, BS; Grant VS Parr, MD, FACC; Gerald Lemole, MD, FACC; Jai B Agarwal, MD, FACC; and Richard H Helfant, MD, FACC. M'd-Atlantic Heart and Vascular Institute, Presbyterian- Univ of Pa Medical Center, Phila, Pa.

Recent studies suggest that patients with 3 vessel coronary artery disease (CAD) and abnormal LV function have better survival rates with bypass surgery compared to medical therapy alone. By excluding crossovers between groups, case control studies may give very accurate survival estimates. To be valid, however, selection biases must be taken into account. Thus, a matched case control method was used to compare survival patterns in medically and surgically treated patients with CAD during the 1980's. Patients with both stable and unstable CAD were entered into a computerized data base and followed for up to 5 years. From this data base, 52 medical patients with potentially operable CAD and 45 surgical patients were matched for significant 3 vessel disease and abnormal LV function. The medical and surgical groups had no significant differences with regard to 21 selected variables including age (64+8 vs. 63+10), chest pain type, symptoms and signs of congestive heart failure, use of cardiac medications, ejection fraction (36+8% vs. 37+9%), segmental wall score, a CAD score evaluating lesion site and severity or comorbid diseases such as hypertension, diabetes, chronic lung disease or peripheral vascular disease. Those patients undergoing coronary bypass grafting had a considerably improved 4 year survival compared to the medical group (88% vs. 54% and p=.03). In conclusion, this study used an effective case control method to suggest that coronary surgery improves prognosis substantially in those patients with severe CAD and LV dysfunction.

CONTINUED IMPROVEMENT IN LATE SURVIVAL AFTER CORONARY BYPASS SURGERY DURING 3 CONSECUTIVE FIVE-YEAR PERIODS
A. Starr, M.D., F.A.C.C., G. L. Grunkemeier, Ph.D. and S. H. Rahimtoola, M.B., F.A.C.C.
St. Vincent Hospital and Medical Center, Oregon Health Sciences University, Portland, Oregon

To determine the relationship between survival and the time-frame of operation, our coronary bypass surgery patients were divided into 3 five-year cohorts:

Years of surgery	1969-73	1974-78	1979-83
Patients	505	1892	2463
Male sex (%)	85	81	78
Mean age (years)	54	58	61
Hypertension (%)	24	31	48
Acute infarction (%)	<1	1	7
Abnormal wall motion (%)	38	40	44
Mean number of grafts	1.8	2.3	2.7
Operative mortality (%)	4.2	1.7	1.6
Follow-up (pt-centuries)	45	122	60

Observed 5-year survival was 85% for the first cohort and 89% for both of the last 2 cohorts. Relative 5-year survival, computed to improve intergroup comparability by adjusting for the changing age and sex distributions, increased greatly from the first (92%) to the second (100%) and slightly for the third (102%). Thus, despite worsening patient risk profiles, more extensive surgical procedures and the use of coronary angioplasty for earlier lesions, late survival following coronary bypass surgery continues to improve.

DETERMINANTS OF SURVIVAL AND ANGINA RECURRENCE AFTER MYOCARDIAL REVASCULARIZATION FOR CONGESTIVE HEART FAILURE WITH ANGINA

Richard J. Shemin MD FACC, Anne C. O'Neil BA, Verdi J. DiSesa MD, Lawrence H. Cohn MD FACC, John J. Collins, Jr. MD FACC, Brigham and Women's Hospital, Boston, MA

The long term benefit of coronary artery bypass surgery (CABG) was studied in 308 patients operated upon for predominant congestive heart failure (CHF) with angina, from the registry of 3,669 patients undergoing CABG from 1970-83. 26 clinical, angiographic and operative variables were analyzed as predictors of survival and recurrent angina using a Cox multivariate model. Operative mortality was 13% (5% elective, 44% emergency). Multivariate predictors for operative death were operative circumstances, need for an intra-aortic balloon, ejection fraction (EF), sex, number of vessels bypassed and left ventricular hypertrophy. The 5 and 8 year (y) survival of operative survivors was 68% and 53%. Multivariate predictors for late survival were EF, number of diseased vessels and postop CHF. Three vessel disease and EF<40 had a 5 & 8 y survival of 59% and 40% vs. 79% and 66% in patients with EF>40. Multivariate predictors for angina recurrence were number of diseased vessels, sex and age. The probability of being free from angina was 71% (2 y), 57% (5 y), and 45% (8 y). At a mean postop interval of 4.5 y, 66% of patients were free of CHF. Although elective CABG has a higher operative mortality risk in patients with CHF, long term angina relief is similar to that for patients without CHF. Improvement in CHF was maintained for up to 5 y in more than half of these patients.

PROGNOSIS OF VENTRICULAR SEPTAL DEFECT FOLLOWING ACUTE MYOCARDIAL INFARCTION. Lemery R MD, Smith HC MD FACC, Gersh BJ MD FACC, Giuliani ER MD FACC, Schaff HV MD FACC, Mayo Clinic, Rochester, MN.

Short-term (one month) and long-term survival were determined in 76 patients (pts) with postmyocardial infarction ventricular septal defects (PMI-VSD). Mean age of 44 men and 32 women was 66 years. MI was anterior in 40 pts and inferior in 36 pts. A history of previous MI was present in 14% and of hypertension in 43%. One month survival was 67% (29 of 43) among pts undergoing surgical repair and 18% (6 of 33) among pts treated medically. Influence of hemodynamic status and timing of surgical repair upon survival are shown below.

GROUP	# pts.	Survival at 1 month: Killip class I-II	Killip class III-IV	Shock
Surgery				
1. <48h	11	2/2	1/1	4/8
2. 48h-14days	6	-	1/1	0/5
3. >14days	26	13/15	8/9	0/2
Total Surgery	43	15/17	10/11	4/15
4. Medical Rx	33	3/6	3/4	0/23
Total All Pts	76	18/23	13/15	4/38

Among medically-treated pts (Group 4), interval between PMI-VSD and hospital death was: 4,4, and 17 days in Killip I-II; 30 days in Killip III-IV; and <2 days for 18 of 23 pts in shock. Five-year cumulative survival in 30-day survivors was 100% in group 1, 54% in group 3 and 33% in group 4.

In conclusion: 1) in pts with shock following PMI-VSD, only those operated within 48 hrs survived, 2) the potential for deterioration as seen in the medically treated pts, plus the excellent surgical results in group 1 pts, warrant early repair for all pts with PMI-VSD.

CLINICAL IMPLICATIONS OF LATE STENOSES IN SAPHENOUS VEIN TO CORONARY BYPASS GRAFTS

Bruce W. Lytle, MD, FACC, Delos M. Cosgrove, MD, FACC, Kirk Easley, MS, Norman Ratliff, MD, Floyd D. Loop, MD, FACC The Cleveland Clinic Foundation, Cleveland, Ohio

From data concerning 501 patients who underwent serial coronary arteriography, first within 5 yrs. of operation for coronary bypass grafting (Study I) and again, more than 5 yrs. after operation (Study II), 80 patients were identified who had a stenotic (not totally occluded) saphenous vein graft (SVG) at Study II and who did not undergo immediate reoperation. In these 80 patients, a total of 144 SVG were surveyed at Study II, of which 34 were angiographically normal, 17 were totally occluded and 93 were stenotic; 56 had stenoses of <50% and 37 had stenoses of ≥50%. Repeat angiography (Study III for 36 patients at a mean interval of 40 mos. after Study II) showed that of 42 stenotic grafts, 16 (38%) were totally occluded, 9 had progression of the stenosis, and 17 (40%) remained at the same level of stenosis. Clinical follow-up at a mean interval of 76 mos. after Study II(range 18-153 mos.) documented that 21 patients had died (mean interval after Study II 36 mos.), 17 myocardial infarctions had occurred (mean interval 37 mos.) and 22 patients had eventually undergone reoperation (mean interval 49 mos.).Five-year event-free survival was 45%. Thirty-two patients with stenotic SVG to the left anterior descending (LAD) had 5-yr. event-free survival of 32% compared with 54% for the rest of the group (p=0.04). Multivariate testing confirmed the adverse influence of a stenotic LAD graft on event-free survival, whereas left ventricular function and degree of vein graft stenosis were not influential. Late SVG stenoses are associated with a high rate of angiographic progression and are predictors of future clinical events. Patients with stenoses in SVG to the LAD are at particularly high risk for clinical events.

THE ROLE OF EARLY GRAFT CHANGES ATTRIBUTED TO INTIMAL FIBROUS HYPERPLASIA IN LATE AORTOCORONARY SAPHENOUS VEIN GRAFT CLOSURE

Simon Kouz, M.D., Lucien Campeau, M.D., F.A.C.C., Jacques Lespérance, M.D., and Martial G. Bourassa, M.D., F.A.C.C., Montreal Heart Institute, Quebec, Canada.

Graft modifications noted at one year were related to late graft closure in a series of 144 patients who had control angiographic examinations within one month of surgery, near one year, and between 2 and 14 years (mean of 8±5 years). Of the 224 patent grafts at one year, 71 had no significant narrowing (32%) and 153 had lumen reduction varying from 20 to 80% when compared to the earlier angiogram. The narrowing was diffuse in 108, focal in 16 or both in 29 and were attributed to intimal fibrous hyperplasia. Graft closure after the first year was observed in 47 of the 224 grafts (21%). Grafts without narrowing had only 6 late occlusions (8.5%) as compared to 41 for grafts showing lumen reduction (27%) p<0.01. In 71 grafts having no diffuse nor focal narrowings ≥20% closure rate was 8.5%, 23.6% in 81 grafts having either diffuse or focal 20-35% narrowings, and 33% in 72 grafts having similar narrowings >35% (p<0.01). It is suspected that grafts with slight to absent lumen reduction also have intimal fibrosis which is not apparent on serial angiograms. Closure rate was higher in grafts having significant lumen reduction between 1 and 7.5 years as well as between 7.5 and 14 years: 17.4% versus 0 (all 31 grafts without lumen reduction remained patent), and 34.5% versus 15% (p<0.05). These observations suggest that minimizing early graft changes compatible with intimal fibrous hyperplasia may retard late graft closure.

Monday, March 10, 1986
2:00PM–3:30PM, Room #267
Effect of Loading Conditions on the Left Ventricle

NONINVASIVE ASSESSMENT OF THE LEFT VENTRICLE AS A PULSATILE PUMP: EFFECTS OF INOTROPIC AND AFTERLOAD CHALLENGES ON VENTRICULAR POWER

Kenneth M. Borow, M.D., Alex Neumann, Sanjeev G. Shroff, Ph.D, Dina Janzen, The University of Chicago, Chicago, IL

Traditional indices of systemic arterial load including SVR describe the heart as a non-pulsatile pump. This may lead to underestimation of total LV load and energetics. Total LV power (TP) incorporates both AO pressure (Pr) and flow variables and therefore can be used as an index of performance of the coupled LV-arterial system. TP can be divided into : (1) steady power (SP) which maintains forward blood flow and (2) oscillatory power (OP) which is lost in pulsations of the arterial system. Although both SP and OP affect LV energetics, only SP results in effective flow. The efficiency of the LV-arterial coupling can be assessed as OP/TP. Efficiency rises as this ratio decreases. We have recently developed a noninvasive method of measuring LV power. AO blood velocity (by continuous wave Doppler) and time-corrected calibrated carotid pulse tracings were simultaneously recorded in 5 normal subjects. AO root size was measured by 2D echo and blood flow calculated. Mean AoPr, CO, SVR, TP, SP, and OP were determined. Data were acquired at baseline, during methoxamine (M), dobutamine (D), and M+D infusions. Percent change from baseline were (*p<.05;+p<.01):

	AoPr	CO	SVR	TP	SP	OP	OP/TP
D	1	17*	-13	23*	18	46+	+18*
M	33+	5	28*	31*	40*	-2	-24*
D+M	25+	14*	11	40+	43+	33*	-6

TP increased with all interventions. Dobutamine increased CO, OP, and OP/TP. Methoxamine increased AoPr, SVR, and SP while decreasing OP/TP. D+M resulted in the combination of these effects with no change in OP/TP.

Thus, (1) TP increased with afterload and inotropic challenges, (2) dobutamine wasted energy in the form of OP thus decreasing efficiency, (3) the traditional indices of arterial load incompletely assess LV performance as a pulsatile pump.

RELATION OF VARIOUS MEASURES OF END-SYSTOLE TO LEFT VENTRICULAR MAXIMUM TIME-VARYING ELASTANCE IN MAN.

Mark R. Starling, M.D., F.A.C.C., Richard A. Walsh, M.D., F.A.C.C., Louis J. Dell'Italia, M.D., John C. Lasher, M.D., and Jack L. Lancaster, Ph.D., Univ. of TX Health Science Center, San Antonio, TX

The relation of various end-systolic pressure (P)-volume (V) measures to left ventricular maximum time- varying elastance (Emax) and extrapolated volume (V_0) at zero P in man are unknown. Thus, 10 patients (7 normal and 3 with aortic regurgitation) without coronary artery disease were studied with simultaneous high-fidelity P and biplane cineangiographic (CINE) V with atrial pacing during control (C), methoxamine (M) and nitroprusside (N) infusion conditions. There was no significant difference in mean heart rate or (+)dP/dtmax between C, M and N. Emax was defined as the maximum linear relation between instantaneous P vs V points at comparable times during C, M and N using frame-by-frame analysis. The slopes, m, (mmHg/ml, r=0.84-1.00) and V_0 values (ml) for the end-systolic P-V relations defined as the maximum relationship of P vs V (maxPV), (-)dP/dtmax P vs V (-dP/dtPV), P vs V at minimum V (minPV) and central aortic dicrotic notch (Aodi) P vs V (AodiPV) compared to Emax are:

	Emax	maxPV	(-)dP/dtPV	minPV	AodiPV
m	5.61±1.74	3.67±1.32+	2.80±1.38*	3.69±1.14+	2.56±1.31+
r	(vs Emax)	0.90	0.57	0.92	0.11
V_0	29±22	7±21+	15±18	7±22+	-2±34*

*p<0.05 or +p<0.01 vs Emax

We conclude that (1) the slopes of the end-systolic P-V relations for these measures of end-systole underestimate Emax, (2) the best correlations with Emax are seen for the maxPV and minPV relations and (3) all V_0 values underestimate that at Emax.

ACCURATE ESTIMATES OF MAXIMUM LV PRESSURE-VOLUME RATIO CAN BE OBTAINED FROM PERIPHERAL DICROTIC NOTCH PRESSURE AND END SYSTOLIC VOLUME

George T. Daughters, M.S., Carol W. Mead, B.S., Edwin L. Alderman, M.D., F.A.C.C., Geraldine C. Derby, R.N., Anne Schwarzkopf, B.S., D. Craig Miller, M.D., F.A.C.C. Palo Alto Medical Foundation, Palo Alto, CA

The maximum value of the ratio of left ventricular (LV) pressure to volume, (P/V)max, useful in assessing the LV contractile state, is sometimes estimated by dividing peripheral arterial dicrotic notch pressure (ADNP) by end systolic volume (ESV) obtained from nuclear angiography or echocardiography. In order to determine the accuracy of such estimates, we compared simultaneously measured values of (ADNP/ESV) and (P/V)max in 27 patients (with normal valvular function) during the first 24 hours following coronary artery bypass graft surgery. LV volumes were assessed by computer-aided analysis of radiographic images of minute tantalum intramyocardial markers inserted at operation, so as to outline the LV in the 30 degree RAO projection. LV and peripheral arterial pressures were measured by micromanometer-tipped catheters. LV pressure-volume diagrams were generated for a total of 208 three-beat sequences under different loading and inotropic conditions. Linear regression analysis showed that values of (P/V)max and (ADNP/ESV) correlated highly (r=0.96). The regression equation was

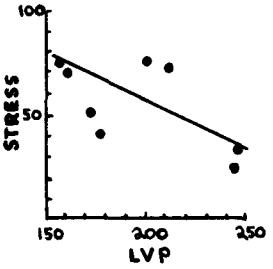
$$(P/V)max = 1.31 \times (ADNP/ESV) + 0.08. \quad (s.e.e. = 0.21)$$

We conclude that a useful estimate of (P/V)max can be obtained in patients without valvular lesions using the ratio of peripheral arterial dicrotic notch pressure and end systolic volume.

IS THERE A FUNDAMENTAL DIFFERENCE IN THE HYPERTROPHY RESPONSE WHEN PRESSURE OVERLOAD IS PRESENT FROM BIRTH RATHER THAN ACQUIRED LATER IN LIFE?

Michael E. Assey, M.D.,F.A.C.C., James F. Spann, Jr., M.D., F.A.C.C., Paul C. Gillette, M.D., F.A.C.C., Blase A. Carabello, M.D., F.A.C.C., Medical University of South Carolina, Charleston, S.C.

Severe childhood aortic stenosis (AS) is associated with "excessive" hypertrophy with resultant low wall stress and high pump performance, while in the adult these parameters are usually normal. We wondered if this reflected a fundamental difference in the hypertrophy (H) response to a pressure overload (P) present from birth rather than one acquired later in life. If a fundamental difference exists, one would expect the childhood pattern to persist with advancing age. To test this hypothesis, we examined ventricular mechanics in 8 children of varying ages (4-19 yrs) with severe AS and in 5 normal children. When compared with normal, AS had significantly reduced wall stress (63±10 vs 122±25, p <.01) and increased ejection fraction (.77±.04 vs .63±.03, p <.05). There was no direct statistical relationship between age and wall stress. There was a significant inverse correlation (r=.60, p<.01) between pressure and wall stress, regardless of age (Fig. 1).



These data support the hypothesis that there may be a fundamental difference in the hypertrophy response when the pressure overload is present from birth rather than acquired later in life.

SYSTEMIC VASCULAR RESISTANCE: AN UNRELIABLE INDEX OF LEFT VENTRICULAR AFTERLOAD

Kenneth M. Borow, M.D., Roberto Lang, M.D., Alex Neumann, Dina Janzen, Dianne Altman, The Univ of Chicago, Chicago, IL

Systemic vascualr resistance (SVR) is a frequently used clinical index of LV afterload. However, SVR reflects peripheral arteriolar tone rather than ventricular fiber force. In contrast, LV end-systolic (ES) wall stress (σ) has been shown to accurately measure LV fiber load. It has been previously assumed that changes in afterload would result in comparable changes in SVR and σ_{ES}. To study this question, 8 dogs were instrumented with central AO microtip and PA catheters. LV wall thickness(WT) and dimensions(D) were measured from 2D- targeted m-mode echo. AO mean(m), RA and LVES pressures, and cardiac output were recorded. SVR and σ_{ES} were determined under control (C) conditions and during 5 µg/kg/min of dobutamine(DB) and 0.1 µg/kg/min of norepinephrine(NE). There were no differences(Δ) in C_{DB} and C_{NE} data. Load independent ES indices of contractility showed DB and NE to be equally potent positive inotropes.

	%Δ(DB)	p-Value	%Δ(NE)	p-Value
AO mean BP	+20	<.05	+35	<.001
CO	+39	<.001	+11	<.05
ES Pressure	+22	<.01	+34	<.01
ES Dimension	-18	<.001	-12	<.01
ES Thickness	+18	<.001	+15	<.001
SVR	-13	<.01	+24	<.001
σ_{ES}	-25	<.01	-8	0.12

For both drugs, ES dimension decreased and ES wall thickness increased counter-balancing the increase in ES pressure. Thus, ES wall stress fell. In contrast, SVR increased significantly with NE and decreased with DB.

Thus, [1] Discordant changes in LV afterload (i.e. ES wall stress) and SVR occur. [2] SVR is an unreliable index of afterload reflecting peripheral arteriolar tone rather than LV systolic wall force. [3] At the infusion rates used in this study, DB and NE have similar positive inotropic effects.

LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION DURING THE GRADUAL DEVELOPMENT OF PRESSURE OVERLOAD HYPERTROPHY.

Peter K Hoshino, MD, Michael R Zile, MD, Alvin S Blaustein, MD, William H Gaasch, MD FACC. Tufts Univ and VA Medical Center, Boston MA

To characterize the relation between LV systolic function and diastolic stiffness during the gradual development of pressure overload hypertrophy (POH), echo and cath data were obtained during the year following the application of aortic bands in 13 puppies. Development of LV pump failure (F) in 6 was manifest by decreased endocardial fractional shortening (FSe,%) and increased end diastolic (ed) pressure (P) (26±6 mm Hg) at 12 mo; 7 remained compensated (C) at 12 mo (normal FSe & edP). Systolic P(F:263±32,C:236±24 mm Hg;p=NS) and LV/body wt (F:9.8±0.9, C:8.3±0.5 gm/kg; p=NS) were similar in the two groups. Midwall systolic stress (MWσ,gm/cm2), shortening (FSe,%) and an index of ed chamber stiffness (CSed,mmHg/cm) were derived from dimension (D,mm), wall thickness (T,mm) and P (mmHg). Data are mean ± SEM. *=p<0.05(F vs C), #=p<0.05(12 vs 6 mo), ©=p<0.05(vs normal).

		COMPENSATED		FAILURE	
	NORMAL	6 mo	12 mo	6 mo	12 mo
Ded	38±1	33±2	37±3	36±2	41±1
Ted	7.2±1	9.7±1©	12.3±1#©	11.8±.4©	13.0±.6©
FSe	39±1	39±4	42±3	36±4	29±2*©
MWσ	256±25	323±42	254±25	318±34	371±46*©
CSed	2.0±0.3	3.7±0.3©	3.3±0.6	4.5±0.9©	6.4±1.5©*

After an early (6 mo) tendency to increase, both MWσ and CSed fell in C but continued to increase in F. Thus, the inability to adapt to pressure overload is manifest by an increased MWσ and decreased FSe (afterload excess) that closely correlates with a rise in diastolic chamber stiffness (independent of changes in Ded, T and mass). This may indicate a change in myocardial properties that affects both systolic function and intrinsic muscle stiffness.

Monday, March 10, 1986
4:00PM-5:30PM, Room #267
Developmental Cardiovascular Studies

AGE-RELATED EFFECTS OF CHRONIC HYPOXIA ON CARDIAC ELECTROPHYSIOLOGICAL FUNCTION. Michael L. Epstein,M.D.,F.A.C.C., Stephen P. Baker,Ph.D.,Philip Posner,Ph.D., University of Flordia, Gainesville, Florida.

We have previously reported, in a 12 week old rabbit model, changes in cardiac electrophysiological (EP) function induced by chronic hypoxia. To determine whether these changes are secondary to the duration of hypoxia, we examined the effect of chronic hypoxia on EP function in younger animals raised in an hypoxic environment.

Eight week old rabbits raised either in normoxia (N) or hypoxia (H) were anesthetized and mechanically ventilated. An intracardiac electrode catheter was used to record the atrial and ventricular electrogram along with a surface ECG. Pacing was performed using a pair of teflon-coated stainless steel wires sutured directly to the RA. The pacing protocol included rapid atrial pacing as well as introduction of progressively premature stimuli into a paced rhythm. Data are presented in milliseconds and are compared as mean ± standard error of the mean. Significance was set at $p<0.05$.

Unlike the differences found between N and H animals at 12 weeks of age, no significant differences were found in the control cycle length (CL), corrected pacemaker recovery time (CPRT), atrial effective or functional refractory periods (AERP,AFRP), or atrioventricular nodal (AVN) ERP in the 8 week old animals.

	CL	CPRT	AERP	AFRP	AVNERP
N	282 ± 11.6	119 ± 2.2	95 ± 3.4	107 ± 3.3	122 ± 7.9
H	342 ± 30.1	115 ± 6.0	88 ± 7.0	103 ± 6.1	132 ± 7.0

Chronic hypoxia did result in a significant difference in the AVN FRP at this age (N=155 ± 3.4 vs. H=172 ± 6.0).

These data indicate that, in this model, the duration of chronic hypoxia is an important factor in causing changes in cardiac EP function.

DEVELOPMENTAL CHANGES IN DOSE AND PLASMA CONCENTRATION OF LIDOCAINE AND QUINIDINE. Yoshiyuki Morikawa, M.D., Allan Hordof, M.D., F.A.C.C., Tove Rosen, M.D., Michael Rosen, M.D., F.A.C.C., Columbia University, New York.

We previously have shown that in intact dogs lidocaine (L) induces greater use-dependent block of intraventricular conduction in the young than the adult, whereas for quinidine (Q), block is equivalent. Here, we report that developmental differences in drug metabolism also contribute to the age-related changes in effects on conduction. We studied 6 adult and 6 10-week old dogs anesthetized with pentobarbital. L was given as IV injections of 3, 6, and 9 mg/kg, followed respectively by infusions of 6, 12, and 18 ug/kg/hr. Q was given as an infusion of 20 mg/kg/hr. The range of total plasma L concentrations [L] = 2.2 - 19.3 ug/ml. Free [L] were measured using a millipore system, and the ratio free/total plasma [L] was determined. The regression line for the adults (slope=.63, r=.96) > the young (slope=.30, r=.77) ($p<.005$). This suggests greater protein binding of L in the young and greater availability of free L at any total plasma [L] in the adult. In contrast, there was no age-related difference in the plasma free/total [Q] over a plasma [Q] range of 2-16 ug/ml. We also related the total plasma concentration of drug to the dose given. For each of the three L dosage schedules, the adult plasma [L] > young [L]. In contrast, there was no difference in the plasma [Q] in adult and young. In sum, the ratio of dose to plasma concentration, and the partition of total/free plasma [L] favors higher free drug levels in the adult. This could explain the greater effect of L on conduction in the adult heart. The ratios for Q are equivalent at both ages, consistent with an equivalent effect of Q on conduction. Hence, differences in L and Q metabolism help explain the developmental differences seen in the effects of both drugs on conduction.

ELECTROPHYSIOLOGIC AND HEMODYNAMIC EFFECTS OF BETHANIDINE SULFATE ON THE IMMATURE MAMMALIAN HEART
Anne Fournier MD, Ming-Lon Young MD, Adrienne Stolfi, Henry Gelband MD, Arthur S. Pickoff MD, University of Miami, Miami, Florida.

Bethanidine sulfate (B), a type III antiarrhythmic agent has proven antifibrillatory effects. B actions on tissue other than the ventricle or on the immature heart are unknown. Utilizing standard intracardiac recording and stimulation techniques, the cumulative electrophysiologic and hemodynamic effects of B (2.5, 5, 10 and 15 mg/kg IV) were studied in 10 canine neonates (age: 5-14 days). Heart rate (HR) increased significantly after the 1st dose (mean ($\bar{m}$): 165 to 188, $p<0.001$) and remained elevated after doses2 and 3. The $\bar{m}$ systolic blood pressure (BP) increased from 54 to 88 mmHg after the 1st dose ($p<0.001$) and remained elevated after all doses. PA, AH, HV, PR intervals andsinus node function did not change. A significant increase was observed in the atrial effective (AERP) and functional (AFRP) refractory periods (RP) following eachdose. The total increase in $\bar{m}$ AERP was from 66 to 154 msec, while the $\bar{m}$ AFRP increased from 108 to 190 msec, $p<0.001$. B enhanced atrioventricular nodal (AVN) function as evidenced by Wenckebach periodicity occuring at a lower cycle length and AVN RP becoming atrial limited. The RP of the ventricle did not change. In summary, in the neonatal canine heart, B enhances AVN conduction, increases HR and BP which may be due to catecholamine release. Most importantly, like other type III agents, B results in a significant prolongation of atrial refractoriness, and thus may be useful agent in treating atrial arrhythmias in the neonate.

FUNCTIONAL AND STRUCTURAL CHANGES IN EMBRYONIC MYOCARDIUM IN A MODEL OF CHRONIC ALCOHOLISM
Roger N. Ruckman, M.D., F.A.C.C., Susan A. O'Brien, B.A., Donna J. Messersmith, B.S., and Dennis E. Morse, Ph.D., Department of Cardiology, Children's Hospital National Medical Center, Washington, D.C.

To investigate functional and ultrastructural changes resulting from chronic exposure to ethanol, chick embryos were injected with one of seven graded doses of ethanol or saline (shams) just prior to incubation, and at 24, 48, 72, and 96 hours post incubation. Cinephotoanalysis was performed on Day 3 at 71 and 73 hours (H-H Stage 19) and on Day 4 at 95 and 97 hours (H-H Stage 22) post incubation. Heart rate (HR) and shortening fraction (SF) were measured from the films. Additional embryos sacrificed at corresponding times were analyzed by electron microscopy.

On Day 3, embryos injected with ethanol doses $\geq$.0375 ml showed a significant increase in HR as compared to shams ($p<.05$). There was an overall increase in mortality over time, with the largest increases among those embryos injected with $\geq$.05 ml ethanol. Among survivors on Day 4, HR showed a plateau with no statistically significant change with increasing dose. In contrast on Day 3, SF, an index of cardiac contractility, decreased with increasing dose. On Day 4, however, SF increased with dose as compared to shams. Electron micrographs demonstrated swelling of mitochondria and margination of nuclear chromatin with increasing dose. However, at all but the highest dose, myofibrils were preserved, which may account for the ability of the embryonic heart to maintain or improve SF.

These data suggest that on Day 3 the embryo's defense against chronic ethanol injury is to increase HR to maintain cardiac output while later in development, on Day 4, survival of the embryo depends on its ability to increase cardiac contractility.

A REVERSIBLE PULMONARY ARTERY BAND.

AP Rocchini, MD, SR Gundry, MD, RH Beekman, MD, FACC, KP Gallagher, PhD, DM Behrendt, MD, FACC, RC Dysko, MD, K Rosen, MD. C.S. Mott Hosp., Univ. of Michigan, Ann Arbor

Pulmonary artery banding (PAB) has become an infrequently used surgical technique; however, if a PAB were developed that could be relieved without the need for open heart surgery, we believed that PAB would be used more frequently in the management of infants with congenital heart disease (CHD). We placed such a PAB in seven 1-week old mongrel puppies by using 4 loops of an absorbable suture material (either PDS or Vicryl). One dog died at 2 months due to right ventricular (RV) failure. The remaining dogs underwent cardiac catheterization and pulmonary balloon angioplasty at 6 months of age. After measuring PA, RV and aortic pressures (P) and performing a RV angiogram, balloon angioplasty of the PAB site was performed in the 5 puppies with significant PA stenosis. A 20 mm balloon angioplasty catheter (Medi-Tech) was used in all dogs. Balloon angioplasty decreased RVP from 101±44 to 42±8 mmHg p<.05, PA to RV systolic gradient from 59±31 to 7±5 mmHg p<.05, and increased the size of the PAB site from 10±3 to 18±1 mm p<.05. All dogs were recatheterized 2 months post balloon angioplasty and then sacrificed. At follow-up catheterization RVP was 51±5 mmHg, PA to RV gradient was 7±5 mmHg and PAB site angiographically measured 18±2 mm. At postmortem examination, there was no evidence of either the band material or PA damage, and the ratio of PAB site to aorta was .88±.05. Although these studies are preliminary, they do suggest that a reversible PAB can be performed. We believe that such a PAB will be used in the future to treat children with CHD.

ECHO DOPPLER COLOR FLOW MAPPING STUDIES FOR ELUCIDATION OF CARDIOVASCULAR ANATOMY AND PHYSIOLOGY IN THE HUMAN FETUS. David J. Sahn, M.D., F.A.C.C., Sandra Hagen-Ansert, R.D.M.S., Univ of Calif, San Diego, CA.

We have performed fetal color flow mapping Doppler examinations on 15 pregnant women between 16 and 28 weeks gestation, all referred for fetal echo because of a major congenital heart malformation in a previous child. All fetuses underwent an anatomical cardiac evaluation with a 5MHz, 128 element dynamically focused large aperature scanner (Acuson) and then had Doppler flow mapping and spectral Doppler performed using a 3.5MHz flow mapping scanner (Irex-Aloka). Especially using low gains to optimize lateral and elevational resolution for the flow signals, unique observations were possible with this new modality of imaging. In 13 fetuses, the phasic patterns of flow and real-time flow diameter of the flow across the foramen ovale from the right to the left atrium could be recorded. The diameter of the foramen flow was 76±13 (SD)% of the aortic diameter and the peak diastolic velocity was 41±12 cm/sec. The flow diameters of the pulmonary artery and the aorta could also be determined in 14 and 13 fetuses, respectively and in 9, the entire aortic arch and flow within it was imaged. In 11 fetuses, the "ductal arch" (PA to PDA to descending aorta) was imaged. Ductal flow diameter was 85±11 % of the aortic root inner diameter. In one fetus referred for a family history of ventricular septal defect (VSD), a 3mm large mid muscular VSD was imaged anatomically and on the flow image, a low velocity early systolic left ventricular to right ventricular shunt was imaged across it. Our study provides, for the first time, normal data for foramen ovale and ductal flow in fetuses. Color flow mapping Doppler while not yet optimized for fetal cardiac imaging appears to allow new aspects of the fetal cardiovascular physiology to be defined noninvasively.

Monday, March 10, 1986
2:00PM–3:30PM, Room #268
Electrical Stimulation and Arrhythmias—Basic Studies

THE THERMAL RESPONSE OF VENTRICULAR ENDOCARDIUM TO LASER AND ELECTRICAL ABLATION AND THE DISPARATE EFFECTS OF DIFFERENT SUPERFUSION MEDIA.

Benjamin I. Lee, M.D., F.A.C.C.; Aldo Notargiacomo, B.S.; Ross D. Fletcher, M.D., F.A.C.C.; E. Rene Rodriguez, M.D.; Victor J. Ferrans, M.D.; Yi-Wang Chen, M.D. VA and Georgetown Medical Centers, and N.H.L.B.I., Washington, D.C. and Bethesda, Md.

Transcatheter delivered laser and electrical energy produces discrete ablation of ventricular endocardium (EN) and may be used to destroy arrhythmogenic foci. To characterize the thermal response (TR) of EN to laser discharge (LD) and electrical shock (ES), and determine the effect of different superfusing media on TR and extent of tissue injury, 57 Nd:YAG LD of 40J and 14 cathodal ES of 200J each were delivered to EN superfused with either whole blood (WB) or normal saline (NS). Tissue temperatures were measured 2mm from the point of contact of the laser fiber or electrode tip to EN. LD produced greater peak tissue temperature elevations in WB (30.1±1.9°C) than in NS (14.7 ±1.0°C) (p<.001) and slower tissue cooling. Resulting EN lesions were larger in WB than in NS (diameter: 3.25±0.22mm vs 1.4±0.1mm; p<.001). Tissue temperatures also rose after ES, however, the magnitude of the increase was smaller than that after LD (p<.001). Unlike LD, peak tissue temperatures and rates of tissue cooling after ES were similar despite superfusion with WB or NS (15±4.7°C vs 14.8±3.1°C; p=NS). In conclusion: 1) Thermal mechanisms play an important role in laser and ES-induced tissue injury, however the degree of thermal injury is greater with laser than with ES ablation. 2) The composition of the surrounding fluid medium influences the thermal effects of LD to a greater extent than those of ES.

ABNORMAL IMPULSE CONDUCTION AND INITIATION ARE PRESENT IN A LARGE BORDER ZONE AFTER HIGH ENERGY ABLATION

Joseph H. Levine, M.D., Joseph F. Spear, Ph.D., F.A.C.C., Harlan F. Weisman, M.D., Charles Prood, M.S., Alan A. Kadish, M.D., Cees de Langen, Ph.D.,E. Neil Moore, Ph.D, D.V.M., F.A.C.C., University of Pennsylvania, Philadelphia, PA.

Arrhythmias may develop following high energy ablation in animals and man. To determine the possible mechanisms of this proarrhythmic effect, 13 epicardial tissues underwent ablation in vitro with 5–40 joules via a 1mm diameter cathode and impulse conduction and action potential characteristics were studied.

Results: Abnormalities in conduction velocity (CV) and action potential duration (APD) were noted in a border zone greater than 10mm x 10mm around the ablation site. Heterogeneity of APD also developed (coefficient of variation (cov) =SD/mean).

	CV (M/S)	APD (msec)	APD-COV (%)
control	0.40±0.17	193.1±24.7	4.0±2.5
post-shock	0.18±0.14	147.3±31.8	18.2±11.0
	p<0.001	p<0.001	p<0.001

In addition, early afterdepolarizations, at times leading to the propagation of extrasystoles, were commonly seen.

Conclusions: 1) Abnormalities in impulse conduction and refractoriness as well as afterdepolarizations are present in a large border zone around the ablation site following high energy ablation. 2) These abnormal electrophysiologic properties may provide an appropriate substrate for arrhythmias.

RECOVERY OF ACTION POTENTIAL AND CONDUCTION AFTER FULGURATION OF SHEEP PURKINJE AND VENTRICULAR MYOCARDIAL FIBERS WITH LOW-ENERGY SHOCKS.

Gilles Lascault, MD, Gérald Nassif, MD, Frédéric Fillette, MD, Yves Grosgogeat, MD, FACC.
CHU Pitié-Salpêtrière, Paris, France.

The effects of fulguration or catheter-ablation on the electrophysiological properties of the conduction system and myocardium have to be further elucidated. In this study, we examined the recovery of the electrophysiological properties of sheep Purkinje and ventricular myocardial fibers after resistive shocks (RS) of 2.6 Joules.

After these RS, the resting potential (RP) of cells located 5 millimeters away from the shock zone was greatly depressed to - 30 to - 50 mV. Return to normal RP was progressive and followed an exponential kinetics. Recovery of conduction was always observed at these shock energies. Whenever conduction resumed the distal action potential (DAP) always exhibited a two-component waveform. The first component was characteristic of a prepotential which suggested an electrotonic type of response. Later on, the DAP returned to a normal pattern with rapid but progressive disappearance of the prepotential.

In conclusion : 1) low-energy RS induce significant but reversible electrophysiological effects, 2) recovery of RP is an exponential phenomenon, 3) conduction blocks secondary to low-energy RS may result from the creation of an inexcitable segment of tissue allowing an electrotonically-mediated conduction before full recovery of conduction.

MODULATION OF SINUS NODE FUNCTION: ROLES OF HISTAMINE IN CARDIAC TRANSPLANT PATIENTS

Andrew E. Epstein, M.D., F.A.C.C., David C. McGiffin, M.D., James K. Kirklin, M.D., F.A.C.C., Basil I. Hirschowitz, M.D., Albert L. Waldo, M.D. F.A.C.C., UAB, Birmingham, AL

Both the native-innervated (ISN) and transplanted-denervated (DSN) sinus nodes function after human cardiac transplantation, providing an opportunity to study SN function simultaneously in the presence and absence of autonomic innervation. Using epicardial wire electrodes placed on the native RA cuff and the donor RA, the responses to histamine (H, 25 mcg/kg/hr IV), diphenhydramine (D, an H_1 blocker, 50-75 mg IV) and cimetidine (C, an H_2 blocker, 4 mg/kg IV) were studied in 8 patients to determine the presence and role of H_1 and H_2 receptors in the SN. The ISN and DSN responded with similar percent changes in cycle length (CL) to H, D, C, and D+C together:

	H	D	C	D+C	*p<0.05
ISN	-16.9%*	0.0%	9.1%	3.6%	
DSN	-15.5%*	2.2%	3.8%	2.9%	

C had both positive and negative chronotropic effects on the ISN in different patients but had either none or a negative chronotropic effect on the DSN. H had a positive chronotropic effect on both the ISN (CL -7.6%, p=0.002) and DSN (CL -6.4%, p=0.005) in the presence of C. However, compared to the baseline response to H, C significantly blunted the response to H only for the DSN. In the presence of D, H did not significantly speed either the DSN (CL -10.8%, p=0.53) or the DSN (CL -2.7%, p=0.50). Conclusions: 1) C and D individually or together do not significantly slow the sinus rate in either the ISN or DSN; 2) the altered responses of the DSN to H in the presence of C or D demonstrates that both H_1 and H_2 receptors modulate human SN function; 3) contrary to prior suggestions, there clearly is an H_1 receptor in the human SN, and; 4) the denervated transplanted heart is a unique model to study SN function in the absence of confounding autonomic nervous system influences.

A DECLINE IN THE VENTRICULAR FIBRILLATION THRESHOLD FOLLOWING SUCCESSIVE PREMATURE EXTRASTIMULI: A MECHANISM FOR INDUCED "ARTIFACTUAL" TACHYARRHYTHMIAS?

Eli S. Gang, MD, FACC, Hrayr Karagueuzian, PhD, Malte Meesmann, MD, Avile McCullen, William J. Mandel, MD, FACC, Thomas Peter,MD, FACC, Cedars-Sinai Medical Center, Los Angeles, CA.

It has been suggested that in some patients the induction of ventricular fibrillation (VF) with 3 or more programmed premature extrastimuli reflects the intensity of the stimulation protocol rather than an inherent ventricular vulnerability. In order to test whether the ventricular fibrillation threshold (VFT) is progressively lowered during programmed stimulation using an increasing number of extrastimuli, we measured the VFT during standard programmed stimulation (at twice pacing threshold current) in 9 normal, anesthetized, closed-chest dogs. The VFT was measured 3 times in each dog: (a) the fibrillating test pulse was placed following a train of 8 paced (S1) beats (VFT-S2), (b) following a single extrastimulus (VFT-S3), and (c) after 2 extrastimuli (VFT-S4). Results: VFT-S3 was 32% lower than VFT-S2 (16±7 mA vs. 24±10 mA, p<0.005). Furthermore, VFT-S4 was 49% lower than VFT-S2 and significantly lower than VFT-S3 (12±8 mA vs. 16±7 mA, p<0.05).

We conclude that during programmed stimulation of the heart, the VFT is progressively lowered by the addition of multiple extrastimuli. This may account for the induction of non-clinical VF, particularly in patients with an already reduced VFT.

ENDOCARDIAL CATHETER ABLATION OF VENTRICULAR MUSCLE INDUCES ARRHYTHMIAS: REENTRY, ABNORMAL AUTOMATICITY, AND TRIGGERED ACTIVITY.

Richard Friedman, MD, Jeffrey P. Moak, MD, Arthur Garson, Jr., MD, FACC, Texas Children's Hospital, Houston, Texas.

Endocardial catheter ablation (ECA) has been advocated for elimination of medically refractory ventricular tachyarrhythmias. Previous studies in dogs have demonstrated the occurrence of ventricular tachycardia (VT), or VT and sudden death in the post-ablative period (PAP). The purpose of our study was to assess the immediate clinical and electrophysiologic (EP) effects of various doses of DC electrical shocks (S) applied to the RV apex (RVA) of puppies (P). Eight beagle P, 2.5-10 mo. (median 8.5) and 3-11kg, (median 9.5) were given S delivered through the distal pole of a USCI tripolar catheter which served as the cathode. Each P received 1 S. Delivered energies were: 400J (3), 200J (4), 100J (1). Six P had 24h of continuous ECG assessment before and after ECA; 2P died after ECA: from ventricular perforation (1) and low cardiac output (1). All 8P developed VT immediately after ECA and of the 6 who lived, all had sustained VT in the 24h PAP. Cellular action potential (AP) characteristics of ablated muscle were studied 24h post-ECA. Results of each ablated P were compared to values obtained from a matched area in the RVA of 4 normals. Maximum diastolic potential was less negative ($p \leq 0.03$) maximum upstroke velocity ($\dot{V}$ max) was lower ($p \leq 0.05$) and AP duration at 50% repolarization (APD50) was longer ($p \leq 0.003$ in 5/6, p=0.07 in 1/6) in ablated muscle. There were also islands of cells with normal AP characteristics in ablated regions. Evidence of reentry (REE) (2P), abnormal automaticity (AA) (3P), and triggered activity (TA) (3P) were seen in cells in ablated regions. We conclude: (1) ECA causes arrhythmias in the immediate PAP due to REE, AA, or TA. (2) ECA does not create a homogenous area of destruction and may leave previously normal or abnormal cells in a viable state.

Monday, March 10, 1986
4:00PM–5:30PM, Room #268
Fibrillation & Defibrillation—Animal Studies

CRITICAL MYOCARDIAL MASS FOR SPONTANEOUS DEFIBRILLATION: EFFECT OF ACUTE ISCHEMIA AND REPERFUSION.
Alexandros C. Kralios, M.D., F.A.C.C. and Fany A. Kralios, M.D., VAMC and Univ of Utah Medical Center Salt Lake City, Utah.

To determine the critical mass (CM) of canine ventricular myocardium able to defibrillate spontaneously (SDF), chloralose anesthetized mongrel dogs 23-27 Kg were placed on right or total cardiopulmonary bypass. With mean systemic arterial pressure maintained at 80mmHg, electrophysiologically isolated, spontaneously beating peninsulas with preserved vasculature were surgically created. After fibrillation (VF) was induced in the peninsula with 50Hz trains of 2ms stimuli, the edges of the tissue were gradually trimmed until SDF occurred. Repetitive inductions of VF lasting at least for 5 sec. and followed consistantly by SDF within 30 sec. were considered as criterion of CM. Subsequently the regional artery of the peninsula was occluded for 3 min. periods and VF inductions were attempted every 30 sec. throughout the occlusion and reperfusion period. Results indicate (1) CM was 21.9 ± 2.5g (n=9) for RV and 23.6 ± 2.6 g (n=4) for LV peninsulas (2) Ischemia did not affect significantly the latency of SDF (control 18.2 ± 1.4 sec. vs. ischemia 22.8 ± 1.5 sec.) (3) Reperfusion delayed SDF for up to 305 sec. (mean latency 200.3 ± 40.5 sec, $p < 0.05$ sec). We conclude that for normally perfused myocardium the CM is larger than anticipated, and is similar for either ventricle although variable among animals. The SDF is not affected by ischemia but is prolonged during reperfusion. These findings suggest that the homogenous perfusion of either control or ischemia favors SDF. Sufficient disparity of perfusion and presumably electrophysiologic properties necessary for sustained VF develop only during reperfusion.

MECHANISMS OF FAILURE OF DEFIBRILLATION
Nitaro Shibata, MD, Peng-Sheng Chen, MD, Ellen G Dixon, MS, Patrick Wolf, BS, Ned D. Danieley, MS, William M Smith, PhD, and Raymond E Ideker, MD,PhD. Duke Univ Med. Ctr , Durham, NC

To see how shocks fail to halt ventricular fibrillation (VF), 41 shocks were given in 7 open-chest dogs during electrically induced VF, while epicardial recordings were made simultaneously from 56 electrodes evenly spaced over both ventricles Unsuccessful shocks (0.01 to 5 J) were given via electrodes on the LV apex and RA, an electrode configuration shown to create an uneven shock field with much higher potential gradients (PGs) in the apical half (APEX) than in the basal half (BASE) of the ventricles. Early sites, defined as an electrode activation time surrounded by later electrode activation times, were identified in maps of the immediate postshock period.

Shock energy groups (J)	Mean No. of early sites		Mean time (ms) from shock to activation at earliest site	
	APEX	BASE	APEX	BASE
A: 0.01-0.05	1.9	3.8*	21	14*
B: 0.1-0.5	0.8	3.4*	39	19*
C: 1.0-5	0.0	3.1*	-	37

*= $p<0.05$ with number to left

Early sites activating ≤ 25 ms postshock suggest failure to halt VF. We have shown with intramural recordings that early sites activating > 25 ms postshock indicate that VF is halted and is then reinitiated by an activation front arising de novo at that site Most PGs at both the BASE and APEX for Group A shocks and at the BASE for Group B shocks were too weak to halt VF Higher PGs at the APEX for Group B shocks and at the BASE for Group C shocks halted VF in that region but then reinitiated it Still higher PGs at the APEX for Group C shocks halted VF without reinitiating it in that region Thus, PGs generated by defibrillation shocks have at least 3 different effects (1) Low PGs fail to halt VF, (2) Higher PGs halt but then reinitiate VF; (3) Still higher PGs halt VF without reinitiating it Successful defibrillation requires a shock strong enough to achieve this third condition throughout the ventricles

QUANTITATED DEPLETION AND REPLETION OF BODY POTASSIUM AND VENTRICULAR FIBRILLATION
Brian McGovern, M.B., Nicolaos E. Madias, M.D., Jeremy N. Ruskin, M.D., F.A.C.C., Vincent J. Canzanello, M.D., John T. Harrington, M.D., Hasan Garan, M.D. Massachusetts General Hospital, Boston, MA

The influence of isolated body potassium (K^+) depletion on vulnerability to electrically-induced ventricular arrhythmias is unknown. We have performed metabolic balance studies in 11 female, mongrel dogs(10-15kg) during which strict control of diet and collection of urine for electrolyte measurements were undertaken. After a control period, dogs were subjected to dietary K^+ depletion and thiazide diuretic treatment. After K^+ depletion, dogs underwent comprehensive electrophysiologic studies (EPS) including programmed cardiac stimulation (PCS) using 1,2, and 3 ventricular premature stimuli in sinus rhythm and 1 and 2 premature stimuli in ventricular pacing. The ventricular fibrillation threshold (VFT) was also determined in each animal. Percutaneous catheter technique with methohexital general anesthesia was used. Following these studies, K^+ repletion was performed by dietary K^+ supplementation until K^+ balance was demonstrated. Results: Mean body K^+ depletion achieved was 63.3 ± 4.1 mEq. The serum K^+ levels during control, K^+depletion and K^+repletion phases were 3.7 ± 0.05, 2.7 ± 0.04 and 4.1 ± 0.05 mEq/l respectively ($p< 0.001$), with no major differences in other measured electrolytes. Ventricular fibrillation (VF) was provoked during EPS in 8/11 dogs during K^+ depletion but in only 1 dog following K^+ repletion($p<0.007$). The mean VFT during K^+ depletion was 33.9±19.2 mA, and rose to 51.5±16.9 mA after K^+repletion ($p<0.003$). We conclude that isolated, severe K^+ depletion significantly increases susceptibility to PCS-induced VF and reduces VFT markedly in this canine model.

DETERMINANTS OF VENTRICULAR FIBRILLATION IN A COMPUTER MODEL OF THE ENTIRE LEFT VENTRICLE.
William M. DeCampli, M.D. and Charles D. Swerdlow, M.D., F.A.C.C., Stanford University, Stanford, CA

We modelled conduction globally in a left ventricle treated topologically as a spherical surface of cells. This differs from all previous computer models which cannot simulate arrhythmias globally because they treat only bounded myocardial regions. Our model's parameters are ventricular diameter (D), mean absolute refractory period (ARP), ARP standard deviation (SDARP), relative refractory period (RRP), and maximum conduction speed (CS_{max}). ARP is distributed randomly; depolarized cells conduct to all nearest cells not in their ARP. CS varies linearly in the RRP, from which mean CS (CS_m) is derived. We studied the effect of 2 extrastimuli at the end of the ARP after an initial stimulus. Integrations were performed for all 256 combinations of these parameter values: D 4, 5, 6, and 7 cm; ARP 175, 200, 225, and 250 ms; SDARP 25 and 50 ms; RRP 25 and 50 ms; CS_{max} 0.4 ,0.6, 0.8, and 1.0 m/s. Integrations stopped after reentrant excitation lasted 15 s or electrical quiescence occurred. The product (F) of 2 dimensionless terms correlated with sustained reentrant excitation:

$$F = [D/(ARP \times CS_m)] \times (SDARP/ARP)$$

The first term in F represents macroscopic conditions for reentry and the second normalized dispersion of refractoriness. Integration results are shown below:

$Fx10^3$	<10	10–15	15–20	20–25	25–30	30–40	>40
Integrations (n)	97	66	37	20	12	14	10
Tachycardia (%)	0	4	22	20	0	0	0
Fibrillation (%)	0	0	0	20	100	100	100

For a normal ventricle, we assumed D=5, ARP=200, CS_m=0.5, SDARP=25, resulting in $F=6.2x10^{-3}$. All ventricles with $F<12x10^{-3}$ recovered. Sustained, organized depolarizations (tachycardia) occurred at intermediate values of F. Higher values produced sustained, chaotic activation (fibrillation). In this global model, vulnerability to sustained reentrant excitation depends on F, a relationship among variables, rather than on the value of any specific variable. This observation may provide insight into the substrate for ventricular arrhythmias in diffuse myocardial disease.

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ESTIMATION OF CARDIAC SURFACE ACTIVATION SEQUENCE FROM BODY SURFACE POTENTIAL MAPS

Haruki Kojima, M.D., Mary Jo Burgess, M.D., Robert L. Lux, Ph.D., J.A. Abildskov, M.D., FACC
University of Utah, Salt Lake City

Activation sequences on the ventricular surface were estimated from selected body surface (BS) electrocardiograms in 7 pentobarbital anesthetized dogs. Up to 50 activation sequences were induced in each dog by stimulating singly and in time-phased combinations from 2 right and 1 left ventricular pacing catheters. 192 lead body surface maps were recorded for each sequence. The chests were then opened, a 75 electrode array placed on the heart and cardiac surface (CS) maps recorded for the same activation sequences. Activation times for both cardiac and body surface waveforms were taken as the times of minimum QRS derivatives referenced to the time of a ventricular stimulus. For each dog, the covariance matrix relating cardiac and body surface times was calculated. A subset of BS sites was selected in the order of importance for estimating CS activation times. A linear BS to CS estimation transformation was then derived from the covariance. Using jackknifing (of each sequence) CS times at 50 CS sites were estimated from times at 3 to 13 BS sites. Correlation between measured and estimated CS times was .95±.025 over all dogs with a range of [.903-.975]. RMS estimation error over all dogs was 7.5±4.4ms. Measured and estimated isochrone maps of CS activation times were consistently very similar. These results support the hypothesis that cardiac surface activation sequence may be sufficiently well estimated from the body surface that non-invasive characterization of cardiac activation sequence is possible.

THE MECHANISM FOR "ENTRAINMENT" AND TERMINATION OF REENTRANT VENTRICULAR TACHYCARDIA BY OVERDRIVE PACING.

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We studied epicardial activation patterns by a multiplexer in 4 dogs post-infarction. In each dog, a reproducible sustained monomorphic reentrant tachycardia was induced in the ischemic epicardial layer. The reentrant circuit had a figure 8 configuration with two circulating wavefronts around two arcs of functional conduction block that coalesced into a slow common reentrant wavefront (CRWF). Overdrive pacing was applied in trains of 2 to 12 beats at different sites around the reentrant circuit. Overdrive pacing at cycle lengths (CL), 10 to 30 msec shorter that the tachycardia CL could perpetuate reentrant excitation. The paced wavefront arrived earlier at the entrance side of the CRWF but conducted slower in this zone. This was consistantly accompanied by modification of the conduction pattern of the CRWF. In other words, there was a change in the reentrant pathway. However, the exit pattern of the CRWF did not change. Following termination of the paced train, reentrant excitation continued and the first post-overdrive CL was shorter than the tachycardia CL. This was due to faster conduction at the zone that showed the slowest conduction during the paced train. When the length of the paced train was kept constant, pacing at shorter CL could terminate reentry. This occurred when the paced wavefront arrived at a strategic zone at the entrance side of the CRWF before refractoriness expired resulting in conduction block. The study shows that perpetuation of reentry at shorter CL by overdrive pacing (so called, entrainment) is associated with subtle but definite changes in the reentrant pathway. The use of the word "entrainment" to describe this phenomenon may not be appropriate.

Monday, March 10, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 4:00PM–5:00PM
Hall D, Georgia World Congress Center
Epidemiology/Prevention

PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN SEX STEROID HORMONES AND CORONARY HEART DISEASE

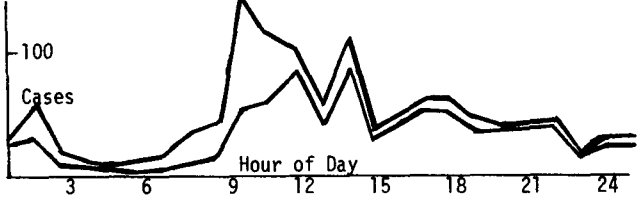
Lewis H. Kuller, M.D., Dr.P.H., James P. Gutai, M.D., Jane A. Cauley, Dr.P.H., Wanju S. Dai, M.D., Dr.P.H.
University of Pittsburgh, Pittsburgh, Pennsylvania.

The relationship between sex hormone levels and subsequent risk of heart attack was studied in a historical cohort study among 163 individuals in the MRFIT Trial who subsequently had a heart attack and 163 controls. Blood samples were collected at baseline prior to randomization. The mean testosterone levels was 789 ng/dl for cases and 771 ng/dl for controls. Androstenedione in 185 ng/dl cases, and 182 ng/dl for controls, estradiol 26.6 pg/dl for cases, 25.9 pg/dl for controls, and estrone 70.6 pg/dl for cases and 72 pg/dl for controls. None of these differences were statistically significant. There were also no differences in ratio of testosterone to estrogens. The testosterone levels were directly correlated with HDLc, LDLc and inversely with obesity. There was a strong relationship between androstenedione levels and cigarette smoking. Data on sex hormone binding globulin will also be presented. The results to date do not support previous case-control studies of a relationship between sex hormone levels and risk of heart attack among men.

CIRCADIAN VARIATION IN THE FREQUENCY OF ONSET OF STROKE

Thomas Robertson, M.D., John Marler, M.D., James Muller, M.D., Thomas Price, M.D., Gordon Lan, Ph.D., Jay Mohr, M.D., Dan Hier, M.D., Philip Wolf, M.D., Louis Caplan, M.D., Selma Kunitz, Ph.D., and the Stroke Data Bank Investigators. National Institutes of Health, Bethesda, MD

Determination that acute vascular events are more likely to start at a particular time of day could facilitate identification of the triggering mechanism(s). A recent study demonstrated greater frequency in late-morning for myocardial infarction. Variation in the onset of stroke by time of day is not established. Using consecutive cases in the Stroke Data Bank (an ongoing multicenter study initiated by the National Institute of Neurological and Communicative Disorders and Stroke), the frequency distribution of the time at which neurologic symptoms were first noted was analyzed for all 1,054 cases with confirmed stroke (see graph--upper line) and for the 692 who did not have neurological symptoms on awakening (lower line). As shown, frequency was low in early morning and high in late morning. Also, in-hospital progression of neurological deficit was more frequent in late morning. These rhythms were observed primarily in ischemic stroke, and this may reflect variation in thrombotic tendency. Conclusion: Stroke appears more likely to develop in the late morning.



CARDIAC FAILURE AND SUDDEN DEATH: THE FRAMINGHAM STUDY

William B. Kannel, M.D., F.A.C.C., Ralph B. D'Agostino, Ph.D., and L. Adrienne Cupples, Ph.D., Boston University Medical Center, Boston, Massachusetts

During 30 years of follow-up cardiac failure (CF) incidence doubled with each decade of age with a male predominance produced by higher coronary heart disease (CHD) rates. Most CF was associated with hypertension or CHD. Among 232 men and 229 women who developed CF, sudden death (SD) occurred at 9 times the general population rate, age-adjusted. In those who also had CHD there was a further doubling of risk.

The major predisposing factors for CF included hypertension, obesity, glucose intolerance, heavy smoking, cardiac enlargement, ECG abnormality and atrial fibrillation. These were also risk factors for SD. These shared modifiable risk factors and cardiac impairments did not entirely account for the markedly increased risk of SD in CF. This suggests that either the damaged myocardium or treatment needed to control the CF may be at fault.

PHYSICAL ACTIVITY, PHYSICAL FITNESS AND CORONARY HEART DISEASE : INCIDENCE DATA IN THE BELGIAN PHYSICAL FITNESS STUDY.

John C. Sobolski, M.D., Marcel D. Kornitzer, M.D. Ph.D., Guy G. De Backer, M.D. Ph.D., Michèle M. Dramaix, M.S., Serge G. Degré, M.D. Ph.D., Henri F. Denolin, M.D. Ph.D. Medical Cardiology Service - Cliniques Universitaires de Bruxelles - Hôpital Erasme - Belgique.

To study the effects of physical activity (Ph.A.) on and off the job and of physical fitness (Ph.F.) on incidence of coronary heart disease (CHD), 2363 Belgian male workers 40-55 years old, entered a 5 years prospective study. Data were collected on established risk indicators and on Ph.A. Ph.F. was derived from a submaximal bicycle exercise test and expressed as the intrapolated PWC 150 or PWC 150/kg, i.e. the work load at heart rate 150/min (per kg of body weight). There were 31 new fatal or non-fatal myocardial infarctions. No significant correlation was demonstrated between quartiles of Ph.A. on and off the job and incidence of CHD. However, the relative risk is almost 2/1 when comparing subjects without to subjects with heavy leisure-time activity (2.1 versus 1.2; N.S.). The incidence of CHD in quartiles of PWC 150 shows a non significant trend (Q1 : 2.18; Q4: 0.75; N.S.). A similar analysis with PWC 150/kg showed a significant trend (Q1: 1.51; Q2: 2.33; Q3: 1.68; Q4: 0.34; $P = 0.05$). The mean PWC 150/kg in CHD /+/ subjects is significantly lower at baseline compared to CHD /-/ subjects (1.34 versus 1.49; $P < 0.03$). In a discriminant stepwise analysis with 9 factors, HDL-cholesterol, smoking and PWC 150/kg discriminate significantly between subjects who will develop CHD and those who remain CHD free. We conclude that in this study, PWC 150/kg, but not Ph.A., is an independent inverse risk indicator of new CHD events.

PSYCHOSOCIAL PROFILE OF PATIENTS FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY (CABGS)

Robin W. Roberts, Ph.D., David W. Coombs, Ph.D., Patrick Whitlow, M.D., F.A.C.C., John B. Wayne, M.B.A., Edgar D. Charles, Ph.D., Ken Bynum, Paula Stanton, Dwayne Crist, Claudina Cabrera. University of Alabama at Birmingham, Birmingham, Alabama.

Seventy-eight patients who received CABGS during 1984-85 were interviewed during the hospitalization in which CABGS was performed and at 3 mo., 6 mo., and 12 mo. post-discharge to determine their psychosocial status and the interaction of psychosocial status and clinical outcomes. Outcome measures include: measures of health status, utilization of medical services, and measures of psychosocial status (depression, social support, health locus of control, stress, and personality type).

At baseline 59% of the patients were depressed and 42% remained depressed at follow-up. Depressed patients were more likely to believe that they were powerless to control their own health and that physicians had more influence over their health situation than themselves. Patients who were depressed had longer lengths of stay, higher relative risk of subsequent cardiac events, lower perceived health status, and were less likely to return to work. Patients who reported a large network of social support were less likely to be depressed, had higher perceived health status, and were more likely to return to work. Preliminary analyses indicate that levels of social support and work status independently and together affect depression. Data suggest psychosocial status influences recovery following CABGS. Identification and counseling of patients with poor psychosocial profiles may facilitate recovery.

LIPID PROFILES AND CORONARY RISK DESIGNATION: IMPACT OF INCONGRUOUS REFERENCE RANGES, VARIABLE LIPID PROFILES, SEX, AND AGE.

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Interpretation of laboratory lipid values in the context of coronary heart disease risk remains obscured by widely variable practices for lipid profile reporting. Of 121 academic clinical laboratories (CLs) surveyed in the United States and Canada, the basis of lipid value interpretation is highly dependant upon choice of reference populations, age and sex of subjects sampled, and lipid parameters utilized for cardiovascular risk specification. Of the 121 CLs, 37 utilized published reports from a specified source, 17 utilized "local" people, 15 utilized "healthy" people, 13 a textbook, 12 a published report of unknown source, 10 a manufacturer insert, 9 unspecified patients, and 4 used their own opinion. Of 105 clinical laboratories, 36 (34%) did not specify age or sex as a determinant in reference ranges, while 36 (34%) specified age only, and 33 (32%) specified both age and sex. Of 41 CLs specifying a cardiovascular risk level for blood lipids, 20 utilized total blood cholesterol (TBC), 14 utilizing high density lipoprotein cholesterol (HDL), and 15 a TBC/HDL ratio. Of CLs utilizing TBC for specification of cardiovascular risk, the cutoff varied from 200 to 330 mg/dl. All but one CL reported a HDL risk of equal to or less than 50 mg/dl and most specified a cardiovascular risk associated with TBC/HDL ratio of greater than 5. Regional differences were present in the 8 geographical areas of continent. The specific lipid value at which cardiovascular risk is specified are inconsistent and misleading, and desperately need a uniform approach to amendment.

HIGH DENSITY LIPOPROTEIN CHOLESTEROL: PROGNOSIS AFTER MYOCARDIAL INFARCTION.

Uri Goldbourt, Ph.D., Lori Mandelzweig, M.P.H. and Henry N. Neufeld, M.D., F.A.C.C., Epidemiology Section and Heart Institute, Sheba Med Center, Tel Hashomer, Israel.

In persons without overt clinical coronary heart disease (CHD), reduced levels of high density lipoprotein cholesterol (HDLC) are a known predictor of a first myocardial infarction (MI), and of death from CHD. In contrast, little is known about the role of HDLC in the prognosis of patients with CHD. We therefore examined, in 130 men with electrocardiographic evidence of myocardial infarction (MI), the relationship of HDLC to prognosis. Approximately 60% (77 men) died between 1963 and 1978, in the bottom HDLC quartile (< 30mg/dl). Quartile analysis was also performed for HDLC as a percent of total cholesterol (PHDL), known as a better predictor of CHD incidence. Mortality was as high as 81% in the bottom quartile (PHDL - 13%), with a relative mortality risk of 1.71 for subjects in the bottom quartile compared to those in the top quartile (PHDL - 19%). Initial mean PHDL in patients surviving 15 years was significantly higher than in those dying during that time (17.8 vs. 16.2%, p <.05). Multivariate analysis, using the Cox proportional hazards model, indicated an association near conventional statistical significance between HDLC and long-term mortality, (p = .069). The results are comparable with those reported by the Coronary Drug Project Study. Further investigations of larger cohorts of MI survivors are needed, before firm conclusions about the role of HDLC and the potential for the use of HDLC affecting drugs or life-style changes can be drawn.

THE CONCENTRATION OF CHOLESTEROL IN SERUM LIPOPROTEINS IN ZEN MONKS

Toru Kita, M.D., Masayuki Yokode, M.D., Masato Kita, M.S., Kazuhiro Fujii, M.S. and Chuichi Kawai, M.D., F.A.C.C., Kyoto University, Kyoto, Japan.

The functional role of the various serum lipoproteins in the pathogenesis of atherosclerosis has become better understood in recent years. It is important to define the environmental factors, especially dietary factors, influencing specific lipoproteins. The concentrations of total, low density lipoprotein (LDL) and high density lipoprotein (HDL)-cholesterol, total triglyceride and apoproteins have been examined in Zen monks whose intake of animal products is almost negligible for 2 to 8 years, and in age-matched (24 to 35 years) control Japanese males who eat western style food. The mean levels of total cholesterol, LDL-cholesterol, apoprotein B and total triglyceride were shown in Table.

	Zen Monks(n=10)	Control Males(n=19)
Total Cholesterol	135.1 ± 15.2*	189.7 ± 17.3
LDL-cholesterol	75.3 ± 12.4*	109.1 ± 18.3
HDL-cholesterol	55.0 ± 14.1**	61.4 ± 13.6
Apoprotein B	62.3 ± 11.0*	94.7 ± 21.2
Triglyceride	43.3 ± 13.5*	72.4 ± 30.3

Mean ± SD *p<0.01 **NS

The mean levels of total cholesterol, LDL-cholesterol, apoprotein B and total triglyceride were 29.8, 31.0, 34.2 and 40.2% lower in Zen monks compared to that in control Japanese males. On the other hand, there was no significant change in the level of HDL-cholesterol in both groups. In this paper, we will discuss these lipid data in association with dietary components.

SUPERVISED PHYSICAL EXERCISE AND DIETARY FAT RESTRICTION IN PATIENTS WITH SYMPTOMATIC CORONARY ARTERY DISEASE: REDUCTION OF STRESS INDUCED MYOCARDIAL ISCHEMIA

G.Schuler MD, G.Schlierf MD, J.Görich MD, A.Dinsenbacher MD, F.Schwarz MD, HC.Mehmel MD, J.Manthey MD, W.Kübler MD, FACC; Medizinische Universitätsklinik Heidelberg, Germany

The purpose of this study was to assess the effect of low fat diet (<20% fat) and daily, supervised training on serum lipoproteins, on physical work capacity (PWC),and on the severity of exercise induced myocardial ischemia (EMI) in patients with symptomatic coronary artery disease (CAD). EMI was assessed by Tl-201 scintigraphy and expressed in degrees of LV circumference; maximal myocardial oxygen consumption was estimated from rate-pressure-products (RPP) during symptom limited exercise. 16 patients were studied before and following 12 months of treatment. Results were compared to 16 patients matched for age and severity of CAD (Gensini score) receiving 'usual care' (CONTROL).

	TRAINING			CONTROL		
	Before	12 months		Before	12 months	
CHOL (mg%)	233±38	197±27	*	239±51	243±65	
TG (mg%)	186±76	130±68	*	179±84	171±55	
PWC (Watt)	152±49	189±52	*	135±24	130±35	
RPP x1000	26 ±5	30 ±4	*	23 ±6	18 ±4	*
EMI (°)	52 ±39	21 ±22	*	47 ±24	48 ±33	

CHOL:Cholesterol, TG:Triglycerides, * p < 0.05 (before vs. 12 months)

CONCLUSIONS: Restriction of dietary fat consumption and supervised physical exercise for 12 months resulted in significant reduction of serum lipoproteins; stress induced myocardial ischemia was significantly diminished despite increased physical work capacity and maximal myocardial oxygen consumption, indicating improvement of myocardial perfusion. In the control group maximal myocardial oxygen consumption decreased, probably as a result of progression of CAD.

PREVALENCE OF MITRAL VALVE PROLAPSE IN NON-CARE-SEEKING ADOLESCENTS.

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In prevalence studies of mitral valve prolapse, selection bias in subject recruitment can limit accuracy when care-seeking patients are included in the study population. To determine the prevalence of mitral valve prolapse virtually free of selection bias, 813 non-care-seeking, demographically heterogeneous sixth grade children from entire school classes, ages 9-14, mean, 11.5 years, were examined in four positions by one or two cardiologists. Mitral valve prolapse, diagnosed when two independent cardiologists concurred on the presence of a mid-systolic click or late systolic murmur, was found in 34 (4.18%), and suspected by a single cardiologist in an additional 32 (3.95%). Cardiologists were unaware of any previous auscultatory findings, the echocardiographic findings or the medical history. Agreement on the diagnosis of prolapse ranged from 78% to 100% among the four pairs of examining physicians. Mitral valve prolapse was found in 25 of 406 girls and 9 of 400 boys (6.16% vs. 2.25%, P<.05). Gender data were missing in 7. Functional murmurs were present in 12 children with mitral valve prolapse and in 539 without (35.3% v. 69.2%, P<.05), but the proportion with third sounds did not differ between the groups. Thus, even among non-care-seeking adolescents where selection bias is minimal, the prevalence of mitral valve prolapse is high. Girls have nearly three times greater prevalence than boys. Functional murmurs were found less frequently when MVP was present.

Monday, March 10, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 2:00PM–3:00PM
Hall D, Georgia World Congress Center
Cardiac Function—Clinical

WHAT IS THE SIGNIFICANCE OF CHEYNE-STOKES RESPIRATION IN SEVERE CHRONIC HEART FAILURE? HEMODYNAMIC AND CLINICAL CORRELATES IN 167 PATIENTS. Stephen S. Gottlieb MD, Paul Kessler MD, Wai Hung Lee MD, Norma Medina RN, Madeline Yushak RN, Milton Packer MD, FACC. Mount Sinai School of Medicine, New York, NY

Cheyne-Stokes respiration (CSR) occurs commonly in states of depressed central nervous system (CNS) function, but its prevalence and pathogenesis in patients (pts) with heart failure (CHF) remains unknown. To determine this, we correlated the occurrence of CSR with simultaneously performed hemodynamic and clinical measurements in 167 CHF pts, none of whom had CNS disorders or received CNS depressants. Cardiac index (CI, l/min/m^2), LV stroke work index (SWI, g-m/m^2), mean arterial pressure (MAP, mm Hg), LV filling pressure (LVFP, mm Hg), systemic vascular resistance (SVR, d-s-c), LV ejection fraction (EF), blood urea nitrogen (BUN, mg/dl), serum creatinine (Cr, mg/dl) and serum sodium concentrations (Na, meq/l), and CSR occurrence were assessed prior to vasodilators in all pts.

CSR was present (+CSR) in 92 of 167 CHF pts (55%), each of whom had periods of apnea ranging in duration from 5 to 60 sec.

	CI	SWI	MAP	LVFP	SVR	EF	BUN	Cr	Na
+CSR	1.6	15	83	25	2138	17	40	1.9	136
-CSR	1.9*	19*	85	25	1930	17	47	2.1	135

Pts with CSR had a significantly lower CI and SWI (* = $p<0.01$) than pts without CSR, but the 2 groups were similar with respect to other hemodynamic variables. Pts with and without CSR did not differ in age (65 vs 63 yrs), BUN, Cr or Na. CSR distinguished pts with a CI < 1.7 l/min/m^2 better than EF, BUN or Cr.

In 12 CHF pts with CSR, the administration of a single dose of hydralazine abolished CSR within 3 hr, and this occurred simultaneous with ↑ in CI and SWI without changes in LVFP or EF.

In conclusion, CSR occurs in the majority of pts with severe CHF, identifies pts with an extremely reduced CI better than other clinical and noninvasive measures of LV function, and can be abolished by vasodilator drugs that ↑ CI.

ATRIAL FUNCTION IN PHYSIOLOGIC AND PATHOLOGIC VENTRICULAR HYPERTROPHY

Vivienne-Elizabeth Smith, M.D., Orysia Tresznewsky, M.D., William B. White, M.D., Mozafarredin K. Karimeddini, M.D., Christopher B. Granger, M.D., Arthur L. Riba, M.D., F.A.C.C., Arnold M. Katz, M.D., F.A.C.C., University of Connecticut, Farmington, CT

Left atrial function in physiologic and pathologic cardiac hypertrophy was evaluated by comparing the relative LA contribution (LAC) to left ventricular end-diastolic volume (LVEDV) in 12 athletes (A), 12 hypertensives (H), and 12 normal subjects (N). LAC was measured from high-resolution, double-gated radionuclide time-activity curves as a percent of LVEDV. Of note, LAC was found to increase with age in a separate group of 45 normals ($R=.48, p<.001$).

GROUP	LVMI(g/m2)	LAI(cm/m2)	LAC(%LVEDV)
N	83 ± 12	1.5 ± 0.2	6 ± 5
A	123 ± 31	2.0 ± 0.2	5 ± 5
H	130 ± 40	1.8 ± 0.2	13 ± 4

Both A and H had significantly increased echocardiographic LV mass index (LVMI). Left atrial dimension index (LAI) was also increased in A and H compared to N (both $p<.001$). LAC was similar in A and N but was significantly higher in age-matched H vs N ($p<.01$). Although LAI was greater in A than H ($p<.05$), LAC was greater in H than in A ($p<.001$).

Atrial function, reflected in the radionuclide time-activity curve as augmented LVEDV, therefore appears to distinguish physiologic from pathologic left ventricular hypertrophy and left atrial enlargement.

QUANTITATION OF AORTIC STIFFNESS IN SYSTEMIC HYPERTENSION

John D. Carroll, M.D., Sanjeev Shroff, Ph.D., Patty W. Arand, BSE, James Rossen M.D., Ted Feldman, M.D. University of Chicago, Chicago, Illinois.

Functionally stiff large arteries may complicate systemic hypertension (HTN) by accentuating systolic hypertension and increasing vascular load . Altered stiffness could be due to the high distending pressure from elevated arteriolar resistance or due to degenerative wall changes. In 5 hypertensive pts we quantitated arterial stiffness by measurements of pulse wave velocity (PWV) from ascending to descending aorta and characteristic impedance (Zc, dyn. sec. cm^{-5}) by averaging impedance moduli between 4-12Hz. High fidelity pressure and velocity sensors (Millar) were used at the time of catheterization. Reduction of distending pressure was achieved with nitroglycerine (NTG,.3mg,sl)

	AOP (mmHg)	PWV(m/sec)	Zc	TPR
Normal Range	60-100	<7	<100	<1200
Control-HTN	126±16	11.1±1.8	240±109	2153±689
NTG-HTN	116±15*	9.5±1.4*	172±67*	1885±777

*$p<0.05$ versus control. AOP=mean aortic pressure. TPR=total peripheral resistance, dyn. sec. cm^{-5}.

CONCLUSIONS: High pulse wave velocity and characterstic impedance both suggest a stiff aortic conduit in hypertension. Thus, both steady load (TPR) and pulsatile load (Zc) are abnormally high. Reduction in distending pressure by vasodilatation with NTG produces a variable decrease in stiffness. This suggests the reversibility of abnormalities in aortic function during therapy in some patients.

LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION AND HYPERTROPHY IN WEIGHTLIFTERS

Anthony Pearson, MD, Michael Schiff, MD, Arthur Labovitz, MD, FACC, Denise Windhorst, George A. Williams, MD, FACC, St. Louis University School of Medicine, St. Louis, MO

Concentric LV hypertrophy (LVH) and asymmetric septal hypertrophy (ASH) have both been described in weightlifters (WL) but diastolic filling, which is abnormal in pathologically hypertrophied ventricles, has not been investigated in such subjects. Accordingly, we performed Doppler and 2 dimensional echocardiography (2DE) on 16 competitive WL and 10 age-matched male controls. Peak (PFR) and mean (MFR) filling rates were determined in cc/sec as the product of the cross-sectional area of the mitral annulus and the peak early and mean diastolic velocities respectively. The flow velocity integrals of the early (Ei) and atrial (Ai) diastolic filling phases were also measured. LV end-diastolic volume EDV and ejection fraction (EF) were measured from the 2DE. WL had significantly higher LV mass, body surface area (BSA) and LV mass corrected for BSA (LVMI, g/M^2). This was due to both increased septum (VS) plus posterior wall (PW) thickness and increased EDV. The ratio of VS to PW in WL was 1.0. There was no significant difference between WL and controls in PFR/MFR, Ei/Ai or PFR.

	VS+PW(cm)	LVMI	Ei/Ai	PFR/MFR	LVEF	EDVI(cc/M^2)
WL	1.89	114±29	2.4±.7	2.1	60	89±19
CONTROLS	1.64	87±15	2.8±.3	2.2	63	72±30
p	NS	<0.02	NS	NS	NS	NS

Ten of the 16 WL had used steroids at some time during their training and use of steroids inversely correlated significantly with indices of diastolic filling (with Ei/Ai, r=-0.65). We conclude that WL have increased LVMI due to both increased EDV and increased wall thickness but no evidence for ASH or abnormalities of systolic or diastolic function.

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PREDICTORS OF EARLY DEATH IN YOUNG TRANSPLANTABLE DILATED CARDIOMYOPATHY

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The selection of candidates for transplant surgery remains a difficult clinical decision. To assess predictors of early mortality (6 months) in relatively young patients (PTS), 67 PTS under age 60 were studied. All PTS had severe dilated cardiomyopathy and were referred for worsening symptoms (NYHA Class III - 18 PTS, Class IV - 49 PTS). There were 34/67 PTS with ischemic heart disease and nonglycoside inotropes were used in 52/67 PTS. Overall mortality was 34/67 (50%) at 6 months. The following characteristics were assessed: sex, age, functional class on admission, functional class on discharge and improvement in functional class, etiology, duration of congestive heart failure, use of antiarrhythmics, pretherapy resting hemodynamics, and arterial norepinephrine (ART NE). Cox step-wise regression identified only ART NE ($p < .04$) and pulmonary capillary wedge pressure ($p < .02$) as significant correlates of survival. Despite the significant correlation, predictive value remains poor. Arterial NE of >500 pg/ml yielded a 67% mortality group and a PCWP of >25 mmHg yielded a 55% mortality group. Similarly, no combination of variables identified a very high or low risk group. The presence of coronary artery disease did not increase risk. We conclude: 1) commonly utilized clinical and hemodynamic variables are of limited predictive value in selection of candidates for cardiac transplantation, 2) other metabolic or morphologic criteria should be sought.

MILRINONE AND DOBUTAMINE EFFECTS ON RIGHT VENTRICULAR PRELOAD, AFTERLOAD, AND SYSTOLIC PERFORMANCE IN CONGESTIVE HEART FAILURE.

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To assess the effects of dobutamine and milrinone on the RV, 14 patients with severe congestive heart failure underwent simultaneous radionuclide-hemodynamic study. Patients were randomized to receive intravenous milrinone (50 mcg/kg bolus then 0.5 mcg/kg/min) or dobutamine (2.5 -15 mcg/kg/min) to achieve equal increases in CO. Drug-induced (steady state) changes in RA pressure, PA end-systolic (ES) pressure, RVES volume, RV end-diastolic (ED) volume, and RV ejection fraction (EF) were recorded (mean ±SE; *$p<0.05$; **$p<0.005$ vs rest):

	CI ($l/min/m^2$)	RA pressure	PAES (mm Hg)	RVES volume	RVED (% change)	RVEF
Rest	2.1±0.3	9±2	37±3			.32±.04*
Dobutamine	2.6±0.3*	9±2	35±4	↓17±6*	↓8±5	.40±.04*
Rest	2.1±0.2	10±2	40±5			.35±.07
Milrinone	2.6±0.1**	9±2	33±5*	↓20±8*	↓9±6	.43±.08*

Neither drug significantly altered heart rate.

Conclusions: 1) In congestive heart failure, both milrinone and dobutamine significantly improve RV systolic performance. 2) For doses used, neither drug substantially alters RV preload, as reflected by RA pressure and RVED volume. 3) For doses achieving similar increases in CO, milrinone effects a greater decrease in RV afterload than dobutamine, as reflected by PAES pressure. 4) Similar improvement in RV systolic function with differential effect on afterload suggests greater RV inotropic effect of dobutamine vs. milrinone.

REGIONAL VENTRICULAR FUNCTION WITH CINE CT

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Employing changes in segmental endocardial contraction (SEC) and segmental wall thickening (SWT) to evaluate regional left ventricular (LV) function requires definition of normal values. Cine CT provides high temporal and spatial resolution which should facilitate evaluation of LV-SEC/LV-SWT. In 11 normal subjects short axis cinetomograms were obtained at the high, mid, and low papillary muscle (PM) level during contrast infusion (mean arterial pressure, 93±10 mmHg; average heart rate, 72±11/min, global LV ejection fraction, 69±7%). At each level the end-diastolic/systolic frames were identified and the epicardial (EP) and endocardial (EN) contours traced. Using both EP and EN centroids contours were divided by computer into 12, 30° radial segments. SEC was calculated from both EP and EN centroids. From each radial segment % LV-SWT was calculated by 3 methods: myocardial radial segment length (SWT1), shortest distance from EP to EN (SWT2) and from EN to EP (SWT3). Results for mid PM level: *$p<.05$ for standard deviation SEC-EN vs SEC-EP.

Method	SEC-EN%	SEC-EP%	SWT1%	SWT2%	SWT3%
Mean±SD	71±8*	72±19	122±204	97±55	105±65

Results were similar at other levels and unchanged by excluding segments containing PM. Due to complex three-dimensional myocardial motion during contraction as well as other technical factors, practical considerations (narrow normal range, ease of analysis) strongly support the use of SEC-EN as opposed to SWT (broad range, difficult analysis) to define regional LV function in patients using cine-CT.

REDUCTION IN FUNCTIONAL MITRAL REGURGITATION BY AMRINONE AND MILRINONE IN SEVERE LEFT VENTRICULAR FAILURE

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The degree to which functional mitral regurgitation is reduced during amrinone or milrinone therapy in patients with severe LV failure is unknown. In 16 patients without primary valvular disease and with severe LV failure {mean ejection fraction 0.16±0.02 (SE)}, we examined the effect of intravenous milrinone (50 μg/kg) or amrinone (3 mg/kg) on thermodilution CO, and simultaneous radionuclide LV output (O). Regurgitant output (RO) was calculated as LVO-CO. At rest regurgitant fraction (RF=RO/LVO) was ≤0.20 in 8 patients (group I) and ≥0.30 in 8 patients (group II; mean 0.49±0.05). Following milrinone or amrinone infusion cardiac output increased 32±9% in group I and 50±7% in group II. Group II regurgitant output and/or regurgitant fraction decreased. Group II (mean±SE):

	CO+	LVO+	RO+	RF
Baseline	1.5±0.2	2.8±0.6	1.1±0.1	0.46±0.07
Amrinone	2.3±0.3**	3.2±0.8	0.9±0.3	0.27±0.08*
Baseline	1.8±0.5	4.0±0.7	2.3±0.9	0.55±0.08
Milrinone	2.5±0.5*	4.0±0.7	1.6±0.8*	0.33±0.17

+$l/min/m^2$; *$p<0.05$; **$p<0.005$ vs. baseline. Mean fractional contribution of reduced RO to the increase in CO induced by amrinone or milrinone was 55±14%. Conclusions: 1) Approximately 50% of patients with severe LV failure have significant functional mitral regurgitation. 2) Bipyridine (amrinone and milrinone) therapy reduces functional mitral regurgitation, and this effect often contributes substantially to the increase in forward cardiac output in patients with severe congestive heart failure.

THE EFFECT OF CHRONIC BETA BLOCKADE ON LEFT VENTRICULAR FUNCTION: LACK OF INFLUENCE OF ISA IN CHRONIC STABLE ANGINA PECTORIS.

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Beta blockers may compromise left ventricular function. Beta blockers possessing intrinsic sympathomimetic activity (ISA) might protect LV contractility. We therefore carried out a study comparing the chronic effects of Propranolol and Pindolol on male patients with stable angina pectoris. LV function was assessed by serial radionuclide ventriculography (RNV), at intervals of 2,6,12,26 and 52 weeks following commencement of beta blockade. Twenty-one patients were allocated to treatment with Propranolol and 19 to treatment with Pindolol. RNV was performed at rest and during cold pressor test (CPT) and during sustained isometric handgrip test (SIHG). Both drugs improved symptoms of angina pectoris by at least one division of the NYHA classification. Resting heart rate (HR) was significantly reduced by Propranolol when compared to basal values ($p < 0.01$ after 6 weeks) as was systolic ($p < 0.01$) and diastolic ($p < 0.05$) blood pressure. Although there was no significant change in resting HR at any time during treatment with Pindolol, both systolic and diastolic BP fell throughout the study ($p < 0.05$ at 6 weeks). Both CPT and SIHG caused increases in HR and BP in both groups throughout the study ($p < 0.01$). During these interventions, the attenuation of heart rate was greater with Propranolol when compared to Pindolol ($p < 0.001$ at 52 weeks). At rest, EF was similar in both groups. During Propranolol treatment this rose sequentially from 49% to 55% at 26 weeks ($p < 0.01$). No change in the resting EF occurred in those taking Pindolol. Small increases in the EF response to SIHG and CPT occurred in the Propranolol group and in the Pindolol group (p = NS). In those with subnormal LVEF (< 50%) resting EF improved significantly throughout treatment with Propranolol rising from a basal value of 30 to 51% at 26 weeks ($p < 0.001$) but not Pindolol. Thus LV function is improved by Propranolol in chronic stable angina pectoris. There is no apparent advantage of ISA in this respect.

ACUTE HEMODYNAMIC AND ANTIISCHEMIC EFFECTS OF INTRAVENOUS DILTIAZEM IN MAN.

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The relation between the antiischemic properties of intravenous (iv) Diltiazem (D) in humans and its acute coronary and systemic hemodynamic effects is incompletely understood. In 15 patients (pts) with coronary artery disease 2 identical pacing stress tests were carried out 30 min before (P1) and immediately after (P2) iv D (bolus of 0.4 mg/kg/min , followed by 0.4 mg/kg/10 min). No untoward effects occurred during and after the infusion. During D infusion a sustained reduction in LV systolic pressure (LVSP,13%), mean aortic pressure (13%) and systemic resistance (SVR,31%) occurred with a 26% increase in cardiac index. In contrast, changes in coronary sinus flow (CSF, increase 21%), coronary resistance (CVR, decrease 28%) and CS O2 content (increase 20%), were shortlasting, only found during the bolus infusion (values $p< 0.05$ vs control). HR, contractility indices, LV enddiastolic pressure (LVEDP), stroke work index and myocardial O2 consumption (MVO2) did not change. During pacing HR were elevated with 10 beats/2 min until angina, block or a maximal HR of 170 beats/min. Although maximal HR were similar during both stress tests and contractility improved during pacing after D, the tension time index was significantly lower during P2 due to a 17% decrease in LVSP, which resulted in a significant reduction in MVO2 (17%) and CSF (12%), as well as in pacing-induced ischemia. The reduction of myocardial ischemia was indicated primarily by normalization of lactate extraction (LE) during maximal pacing HR (LE: - 22±9,7% (P1) vs 6±5,3% (P2)) and by a significant reduction in L production 15 seconds after pacing (LE: -50±12% (P1) vs -6±7,8% (P2)). Moreover , ST segment depression was less during pacing (0,23±0,02 mV(P1) vs 0,13±0,01 mV (P2) and LVEDP post-pacing reduced (28±3 mmHg (P1) vs 13±2 mmHg (P2), whereas angina, present in all pts during P1, was absent in 7, less in 6 and similar in 2 pts after D. Thus,in humans, high doses of D induce sustained reductions in SVR, equivalent but shortlasting changes in CVR and improve pumpfunction without changes in HR and contracitlity. D has antiischemic properties due to sustained peripheral vasodilation resulting in decreased myocardial O2 demand and consumption.

THE HAEMODYNAMIC EFFECTS OF QUINAPRIL, A NON-SULPHYDRYL A.C.E.-INHIBITOR, IN PATIENTS WITH CARDIAC FAILURE

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We studied the effects of Quinapril(CI-906) a new non-sulphydryl A.C.E.-inhibitor in 10 patients with cardiac failure, NYHA class 3-4 (9M and 1F aged 43-70 yrs). Seven had ischaemic heart disease, 2 had congestive cardiomyopathy, and 1 had corrected transposition. All patients gave informed consent. A Swan-Ganz thermodilution catheter was inserted and the right atrial (RA), pulmonary artery (PA) and pulmonary artery wedge (PAW) pressures, plus cardiac output (CO) measured. Following Quinapril 5 mgs orally pressure measurements, CO, heart rate and BP were measured at 15 mins intervals for 3-4 hrs. Nine patients then continued into the chronic study receiving Quinapril 5 mgs tds (1 pt withdrew). Non-invasive investigations continued monthly. Results from the acute study showed maximum effects 1-2 hrs after drug administration. Mean BP fell from 93-83 mmHg, mean PAW fell from 30 to 14 mmHg while mean CO rose from 3.5 to 4.4 l/min. Mean systemic vascular resistance (SVR) fell from 2010 to 1300 dynes. Effects on BP, CO and SVR continued 4 hrs; PAW values returned to the pre-treatment values at 4 hrs. In the chronic study, 6 of 9 patients have done well with improvement in effort tolerance (follow-up 2-5 months). Drug therapy was discontinued in 3 patients, 1 with a pronounced diuresis after 48 hrs therapy, who became dehydrated, 1 who had a further myocardial infarction and 1 who developed significant hypotension. Thus although considerable haemodynamic improvement occurred in all patients acutely, hypotension may develop during chronic therapy and great care must be exercised with additional diuretic treatment.

DOES DIGOXIN IMPROVE EXERCISE CAPACITY IN CHRONIC CONGESTIVE HEART FAILURE?

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The ability of cardiac glycosides to improve exercise tolerance in patients with congestive heart failure (CHF) is highly controversial. Twelve ambulatory patients ages 46-70 years (x = 57.8) with chronic stable CHF, systolic left ventricular dysfunction (ejection fraction = 33 ± 12) and sinus rhythm performed maximal treadmill exercise after four weeks of digoxin or placebo administered in a randomized crossover protocol. Serum digoxin level averaged 1.4 ± 0.3 ng/ml during the digoxin phase. Exercise duration (min.), peak oxygen consumption (VO_2, ml/kg/min), maximal heart rate (MHR, beats/min), oxygen (O_2) pulse (peak VO_2 ÷ MHR), minute ventilation (Vent, liters/min) and ventilatory equivalent (Vent Equiv, Vent ÷ total body VO_2) are shown below. There was no significant difference between digoxin and placebo in any parameter by paired t test.

	Digoxin	Placebo	Difference
Duration	7.9 ± 2.3	7.7 ± 2.6	0.2 ± 1.0
Peak VO_2	19.3 ± 4.6	18.7 ± 5.4	0.6 ± 4.2
MHR	141 ± 19	143 ± 23	-2 ± 12
O_2 pulse	10.5 ± 2.0	9.7 ± 2.6	0.8 ± 1.7
Vent	40.5 ± 11.8	41.5 ± 12.4	-1.0 ± 9.5
Vent Equiv	29.2 ± 4.6	31.1 ± 6.1	-1.9 ± 5.6

Therefore, in ambulatory patients with stable chronic CHF, systolic left ventricular dysfunction and sinus rhythm, digoxin has no discernible beneficial effect on aerobic exercise performance.

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SUBCOSTAL TWO-DIMENSIONAL ECHOCARDIOGRAPHIC IDENTIFICATION OF ANOMALOUS ATTACHMENT OF SEPTUM PRIMUM IN PATIENTS WITH LEFT ATRIO-VENTRICULAR VALVE UNDERDEVELOPMENT

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A new type of atrial septal defect (ASD) has been described in association with hypoplastic left heart syndrome - the septum primum (flap valve of foramen ovale) attaches directly to the postero-superior LA wall, far to the left of the septum secundum. We examined 43 infants with left atrioventricular valve (LAVV) hypoplasia or atresia using subcostal 2-dimensional echocardiography (long axial oblique atrial views) to determine the incidence of such "malalignment-type" ASD's. Twelve of 26 (46%) with normally related great arteries, 9/13 (69%) with double-outlet right ventricle, and 2/4 (50%) with TGA, single LV, and subaortic outlet chamber had malalignment-type ASD's, which were usually restrictive in size.

We conclude that leftward malalignment of the superior attachments of septum primum occurs frequently in patients with LAVV underdevelopment, regardless of the type of conotruncus. Complications associated with ASD enlargement such as perforation of the LA wall during attempted balloon or blade atrial septotomy are understandable in the setting of septum primum malalignment. Because of the anomalous attachments of the septum primum, the atrial septal configuration would tend to guide a catheter straight toward the postero-superior LA wall rather than toward the body of the LA. Recognition of this atrial septal anomaly is especially important when performing atrial septectomy as part of the Norwood procedure for hypoplastic left heart syndrome.

CYSTIC MEDIONECROSIS IN COARCTATION OF THE AORTA: A POTENTIAL FACTOR CONTRIBUTING TO ADVERSE CONSEQUENCES OBSERVED FOLLOWING PERCUTANEOUS BALLOON ANGIOPLASTY OF COARCTATION SITES.

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Percutaneous balloon angioplasty applied to sites of aortic coarctation (C) has generally resulted in improved luminal patency, but has been complicated by an unacceptable incidence of adverse consequences, including anuerysm formation at or near the site of attempted dilatation. We have recently observed that cystic medionecrosis (CMN) is a predictable histologic consequence of iatrogenic aortic C in a dog model of aortic C. To determine if CMN might similarly be observed in humans with C, we reviewed the histologic sections prepared from resected portions of aorta in all patients in whom such specimens had been preserved following attempted surgical repair of aortic C (14) and in one patient with non-repaired aortic C studied at necropsy. A total of 1 to 7 sections from the surgical specimens and 24 sections from the necropsy specimen were stained with Verhoeff's elastic tissue stain and alcian blue, and evaluated according to a scale of 0 to 4+ for depletion and disarray of elastic tissue; and pseudocyst formation accompanied by increased glycosaminoglycans ground substance. If both findings were present and graded as $\geq$ 2+, then the histologic diagnosis of CMN was considered to be satisfied. Results: CMN was observed in each of the 14 resected surgical specimens and in the necropsy specimen as well. In the latter, CMN was present at the C site and extended 3 cm. proximal and 2 cm. distal to the C site. Conclusion: these findings suggest that CMN of the aorta is a consistent histologic feature of C of the aorta. This finding may explain not only the high frequency of adverse results observed following attempted angioplasty of aortic C, but also the known association of aortic dissection and aortic C.

BALLOON DILATATION ANGIOPLASTY FOR COARCTATION OF THE AORTA IN INFANTS.

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Operation for aortic coarctation in (CoA) infancy may be a lifesaving procedure but it still carries a high mortality and is frequently followed by recurrence of stenosis. This recurrence of stenosis is more common when the surgical procedure is performed in the first 3 months of life. Balloon dilation angioplasty (BDA) was successfully performed in 10 patients ages 11 to 30 days (median 14 days) with CoA; PDA was present in 8, a small VSD in 3, ASD in 1, and subvalve AS in 1. Each patient presented in severe congestive heart failure. The balloon diameter ranged from 3.5 to 5.0mm on a 4.2 to 5 French shaft. Selection of balloon diameter was based on angiographic measurements of the aortic isthmus at the base of the subclavian artery. The dilatation was performed 3-4 times at 6-8 atmospheres (90-120 pisi). The pre-dilation systolic pressure gradient (ΔP) was 25 to 88, (mean 54)mmHg) and post dilatation Δ P was 0 to 30, (mean 7)mmHg). No serious intraprocedural complications occurred. The CoA was not totally relieved with a persisting waist in most patients, but allowed these infants to clinically improve and grow to an age at which surgical repair may be performed at a much lower morbidity and mortality risk. With follow-up of 2 to 9 months, 5 patients had recurrence of CoA clinically and 2 required surgery 4 and 7 months later. One patient had CoA repair and pulmonary artery banding for unrelieved CHF 2 days post BDA. BDA is a safe, effective, palliative, nonsurgical alternative for the treatment of discrete coarctation in infants. Refinements in small balloon design might improve the long term results of BDA in infants.

HAZARDOUS BY-PRODUCTS OF LASER IRRADIATION - A QUALITATIVE AND QUANTITATIVE STUDY

Giora Ben-Shachar, M.D., Michael L. Spector, M.D., Dennis E. Morse, Ph. D,, Merril E. Adams, Ph. D., Mark C. Sivakoff, M.D., Thomas A. Riemenschneider, M.D., Case Western Reserve University, Cleveland, and Dept. of Anatomy Medical College of Ohio.

Laser Irradiation (ALI) of cardiac tissues in blood medium can create hazardous products such as tissue debris, thrombus, gas and temperature changes. The purpose of this study was to quantitate the amount of these hazardous by-products. Fresh segments of porcine vascular walls and myocardium were irradiated in-vitro with continuous ALI in sodium phosphate buffer. The amount of tissue loss and debris formation was measured and analyzed with Scanning Electron Microscopy. Artificial circulation utilizing centrifugal pump (Bio-Medicus 520D) ALI irradiation chamber and downstream temperature probe chamber were constructed and heparinized blood was circulated @ 2L/min. ALI irradiation with 400 mic fiber at 6 1/2 watts and 400 mic hot-tip for 10 min. each were performed. Temperature changes at lasing site and downstream chamber, and thrombus and gas formation were measured. Vascular walls and myocardial debris formed at a rate of 227 and 61.5 mg respectively per 1,000 mg tissue lased, showing charred fragmented tissue segments on SEM with sizes ranging up to 3 mm. Fragments of cell wall, and intracellular membranes were also identified. 23.5 and 15.5 ml of gas were formed by both fiberoptic and hot tip irradiation respectively. Temperature elevations were between 1 and 3.9°C in lasing chamber and 1 and 2°C in downstream chamber. 15x5 and 6x4 mm charred thrombi formed at catheter tip respectively regardless of anticoagulant used. Fiber tip melted during irradiation exposure and its length was shortened significantly. In conclusion: very significant amounts of gas, tissue debris and charred thrombi were formed during continuous lasing process to the extent that modifications in laser technique and application must be developed before laser therapy can be applied in clinical settings.

EXERCISE HEMODYNAMICS AFTER A FONTAN PROCEDURE

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To assess exercise hemodynamics after a Fontan procedure, 8 patients (2 tricuspid atresia, 6 single ventricle) underwent cardiac catheterization 16 mo. (mean) postoperatively. Supine bicycle ergometry was performed in 6; all 8 underwent atrial pacing. CI, PA 0_2 saturation, mean PA pressure, and systemic blood pressure were measured at baseline, during pacing, and, in 6 patients, at peak exercise.

Peak pacing heart rate (158 BPM, mean) was significantly ($P<0.05$) greater than peak exercise heart rate (132 BPM, mean). Exercise CI increased 96% (P 0.01) from 2.4 L/min/m^2 (mean, rest) to 4.7 L/min/m^2 (peak exercise). Pacing CI decreased 12% ($P<0.01$) from 2.4 L/min/m^2 (rest) to 2.1 L/min/m^2 (paced). Rest PA 0_2 saturation (68%) decreased significantly ($P<0.01$) at peak exercise (33%) but not during pacing (64%). Exercise mean PA pressure (21 torr) increased by 50% (rest=14 torr) compared to 14% increase with pacing (16 torr). With exercise, mean systemic blood pressure increased 16% from 86 torr (mean, resting) to 100 torr (mean, peak exercise). Mean systemic blood pressure was unchanged by pacing (72 torr mean, rest; 75 torr mean, peak exercise).

Patients after Fontan procedure undergoing supine bicycle ergometry during cardic catheterization display an inordinate increase in their PA pressure and decrease in mixed venous 0_2 saturation relative to the increase in CI and workload. That atrial pacing did not reveal increased CI relative to PA pressure increase suggests that CI in these patients is more sensitive to increased venous return from exercise than heart rate.

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POTENTIAL SOURCES OF ERROR IN DETERMINATION OF DOPPLER CARDIAC OUTPUT IN PEDIATRIC PATIENTS

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To assess potential errors in the estimation of cardiac output in children by continuous wave Doppler we examined the effect of variations in site of measurement of aortic dimension and changes in hemodynamic variables on the correlation of continuous wave cardiac output (CW-CO) with simultaneous thermodilution cardiac output (TD-CO). Aortic diameter was determined in systole from two-dimensional long axis echocardiograms at the aortic valve anulus, ascending aorta 2 cm above the sinuses of Valsalva, and aortic root at the sinuses of Valsalva. We performed 27 CW-CO measurements of aortic flow velocity in 12 pediatric intensive care patients (age 7 mos-16 yrs; weight 7-80 kg). Twenty-two serial studies were performed in 7 patients. All were receiving inotropic or afterload reducing agents.

Results: The range of TD-CO was 1.1-6.3 l/min. CW-CO and stroke volume were linearly related to TD-CO and stroke volume ($r=0.94$, TD=1.02CW + 0.84, SD=0.45 l/min, $p<0.001$). Calculation of CW-CO from aortic valve anulus diameters gave the best correlation ($r=0.94$). In serial studies variations in systemic vascular resistance (694-4972 $U \cdot m^2 \cdot cm^{-5}$) and in heart rate (103-190) did not affect the strength of the correlations. CW-CO and TD-CO correlated well on serial examination of individual patients. We conclude that CW Doppler reliably estimates cardiac output and stroke volume in infants and children even in the presence of variations in systemic vascular resistance and heart rate. The use of aortic valve diameter to calculate CW-CO gave the best correlation with the smallest error.

IN VIVO EVALUATION OF THE CONTINUITY EQUATION FOR ESTIMATION OF MITRAL VALVE ORIFICE AREA

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The continuity equation equates the product of mean velocity multiplied by flow path area for two or more areas of the circulation under the conditions of constant flow. Measurement of mitral valve orifice area (MVA) remains a time-consuming method. The purpose of this investigation was to determine the relationship of (MVA) measured by the elliptical method (EM) and estimated by the continuity equation as based on Doppler or Fick AO flow and mitral mean velocity. The population consisted of 34 individuals (17 normals and 17 patients with various forms of cardiac diseaes, none of whom had AO or mitral regurgitation or shunts that would affect AO and mitral flow differently). AO velocities and vessel dimension were measured from the suprasternal notch with an off-axis transducer; CO was computed as the product of vessel area and mean velocity. The mitral annulus was imaged in short axis and MVA was computed according to the published elliptical method. Maximal mitral spatial velocity, without angle correction, was measured from the apical view. Mitral mean velocity and AO Doppler flow were used in the continuity equation to compute MVA. Mean MVA by EM was 4.82 cm^2 (2.2 SD) and by the continuity equation was 4.96 cm^2 (2.5 SD)($p=ns$). The correlation of the two had a value of +.94 (.72 cm^2 SEE). For the 8 patients who had Fick flows at catheterization the correlation was +.95 (.35 cm^2 SEE) and MVA means were 3.42 cm^2 (1.4 SD) as derived from Fick flows and 3.17 (1.5 SD) for areas derived by the continuity equation ($p=$ ns). These results demonstrate in vivo that the continuity equation accurately estimates MVA under the conditions of absence of AO and mitral regurgitation, absence of shunts which would affect mitral and AO flow differently, and availability of mitral velocity and AO flow.

CORRELATES OF RESTING AND MAXIMAL EXERCISE SYSTOLIC BLOOD PRESSURE LEVELS AFTER REPAIR OF COARCTATION OF THE AORTA.

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It has been demonstrated that repair of coarctation of the aorta may not prevent the subsequent development of elevated systemic blood pressure and the associated premature morbidity and mortality. We investigated the correlates of resting (RSBP) and maximal exercise (EXSBP) systolic blood pressure in 42 patients who had graded exercise tests (ET) after correction of coarctation of the aorta. The age at surgery was 105.9 ± 48.4 months (mean ± SD). The age at exercise test was 161.9 ± 53.0 months. Multiple regression was used in the analysis. The regression model which best explained the variance of each dependent variable and included regression coefficients which were significantly different from 0 ($p \leq .05$) was selected. The independent variables investigated included height (HT), weight, body surface area, age at surgery, age at ET, interval between surgery and ET, highest systolic blood pressure measured prior to surgery (POSBP), gradient across the coarctation measured at preoperative cardiac catheterization and the residual gradient (RESG) measured at cardiac catheterization in those patients where residual coarctation was suspected clinically. The same combination of independent variables provided the best regression model for both RSBP and EXSBP. The models were RSBP = 27.25 + 44.36 x HT + 0.19 x POSBP + 0.47 x RESG ($r^2 = 0.45$) and EXSBP = 87.8 + 126.84 x HT + 0.53 x POSBP + 1.31 x RESG ($r^2 = .71$). None of the other independent variables, including age at surgery, added significant explanatory ability to either model. We conclude that increased preoperative systolic blood pressure and postoperative residual gradient are important correlates of elevated postoperative RSBP and EXSBP. Corrective surgery for coarctation may be deferred in asymptomatic children, as long as blood pressure remains normal, until an age when repair is less likely to result in recurrent coarctation.

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THE RELATIONSHIP BETWEEN MYOCARDIAL DYSFUNCTION AND CORONARY ANEURYSMS IN KAWASAKI DISEASE. Julian M. Stewart, MD PhD, Paul K. Woolf, M.D. Paul Burleson BA, Michael H. Gewitz, MD FACC, NY Medical College, Valhalla, New York.

LV dysfunction (LVD) occurs in children with Kawasaki Disease (KD) with coronary aneurysms (CA) and may appear in pts. without CA as well. In order to noninvasively detect LVD early in KD we developed computerized M-mode echocardiographic methods to assess systolic and diastolic phase indices normalized for heart rate and ventricular size and compared pts. with and without CA.

32 patients were studied, 10 with KD and 22 age-matched controls without heart disease. KD was diagnosed by the presence of at least 6 classic criteria. Controls were divided into 10 febrile pts. and 12 afebrile. All KD pts. had at least one echo in the acute phase and a second during convalescence (1-6 months later). KD ages ranged from 18 mos. to 8 yrs. and were divided into 2 groups based on the presence (+CA)(N=5) or absence (-CA)(N=5) of CA. Peak rate of LV shortening (PRS) and peak rate of LV relaxation (PRR) were computed from standard M-mode echo and normalized for R-R interval and LV size. Percent LV shortening (%S) was also calculated. For controls, results did not depend on the presence of fever. All but one KD patient (+CA and in overt heart failure) had %S not statistically different from controls. Acute PRR was significantly less than control (p .05) for both (+CA) and (-CA) groups. (+CA) pts. had greater reduction in acute PRR than (-CA) pts. During convalescence PRR became normal for all (-CA) pts. but remained low for (+CA) pts. (p .05). Acute and convalescent PRS for (-CA) were not significantly different from control but acute PRS was significantly decreased in (+CA)(p .05). During follow-up PRS increased to normal in all (+CA) pts.

These data suggest: 1) systolic and diastolic phase indices are abnormal in KD pts. with CA and at follow-up diastolic relaxation remains impaired. 2) Diastolic phase abnormalities may be present acutely in KD pts. without CA but disappear at follow-up. 3) Pts. with KD have LVD even without CA but the duration of LVD is increased in the presence of CA.

CONDUCTION SYSTEM IN CASES OF SUDDEN DEATH IN CONGENITAL HEART DISEASE MANY YEARS AFTER SURGICAL CORRECTION
Saroja Bharati, M.D., F.A.C.C. & Maurice Lev, M.D.,F.A.C.C. Deborah Heart & Lung Center, Browns Mills, New Jersey

The conduction system (CS) and the entire heart were examined histologically in four patients with congenital heart disease (CHD) who had surgery many years before they died suddenly. All were asymptomatic, in sinus rhythm and living normally. Case 1, a 23 year old male had a Hancock prosthesis from RV to the pulmonary trunk, for tetralogy of Fallot with pulmonary atresia at the age of 17. Case 2, a 20 month old male child had a Senning for transposition at the age of 8 months. Case 3, a 30 year old female had an ostium primum repaired at the age of 13. The fourth case, a 9 year old boy had a Hancock prosthesis from the RV to the pulmonaries for double outlet LV at the age of 5. All hearts were enlarged with fibroelastosis. CS revealed in case 1, fibrosis and fatty infiltration (FI) of the approaches to the SA, AV nodes, edema of the atrial septum, AV node and AV bundle (AVB) with mononuclear cells, a left sided AVB, dissolution of parts of the AVB and LBB, marked fibrosis of RBB, fibrosis of the LV and RV. Case 2 revealed chronic myocarditis, mostly the infundibulum of RV and the AV node, and a left sided AVB. Case 3, showed FI, fibrosis of the approaches to the SA and AV nodes, atrial septum, AVB, and fibrosis of the bundle branches and the right side of the septum. Case 4, revealed inflammatory changes in the approaches to the SA node, in the atrial septum, AV node, AVB and the right side of the septum. The penetrating AVB revealed loop formation. The branching AVB was left sided. In summary, our study reveals that fibrotic scar areas and chronic inflammatory cell infiltrates in the CS and the surrounding myocardium are seen after surgery. This may be associated with myocarditis. These pathologic findings may form an anatomic substrate for arrhythmogenicity and sudden death in some cases.

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HEART DISEASE IN BASIC TRAINEES WITH CHEST PAIN
Wesley Covitz, M.D., F.A.C.C., Albert C. Molnar, M.D., Casimir Eubig, Ph.D., Etheridge J. Lovett, M.D., James Christiansen, M.D., Medical College of Georgia, Augusta.

Basic trainees who sought medical attention for chest pain were systematically evaluated to detect heart disease and identify risk factors. The 218 subjects enrolled were drawn from a potential population of 14,000 trainees (1.6%). They were equally divided by sex and race. Their mean age was 21 ± 3.8 years. The evaluation consisted of a brief screening exam (phase I), a comprehensive history and physical (phase II) and echocardiography and exercise radionuclide ventriculography (phase III). Phase I exams were sufficient to exclude heart disease in 114 trainees (52%). An additional 54 subjects (25%) were returned to duty after phase II. Of the 50 soldiers who entered phase III 20 were found to have cardiovascular disease (9% of total group). The most common noncardiac causes of chest pain were musculoskeletal 104 (48%) and respiratory 27 (12%). Angina was an infrequent complaint 8/218 (4%) but 3/8 had significant heart disease. The most frequent reasons for referral to phase III were exercise induced syncope (20/50), suspected mitral valve prolapse (10/50), and heart murmur (9/50). Mitral valve prolapse was confirmed in 15/20 trainees with heart disease. Of those with prolapse, 7 had exercise induced syncope, one had exercise induced ventricular arrhythmia, and one had a hypertensive response to exercise. The 5 subjects without prolapse had exercise induced hypertension(2), 2° heart block with inadequate heart rate response to exercise, exercise syncope with subendocardial ischemia, and exercise syncope with abnormal take off of the left coronary. Angina, symptomatic mitral valve prolapse, and exercise induced syncope were important predictors of heart disease in basic trainees with chest pain.

PLASMA NOREPINEPHRINE AS AN INDICATOR OF CONGESTIVE HEART FAILURE IN INFANTS AND CHILDREN.
Robert D. Ross, M.D., Stephen R. Daniels, M.D., David C. Schwartz, M.D., F.A.C.C., David Hannon, M.D., Samuel Kaplan, M.D., F.A.C.C., Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

Plasma norepinephrine (PNE) is usually elevated in adults with congestive heart failure (CHF) and reflects increased sympathetic nervous system output. This finding has not been tested in infants and children who, unlike adults, frequently have a large left to right shunt from a congenital defect as the cause of the CHF. We studied 70 patients (mean age 4.0 years, range 1 month-14.5 years) with a variety of cardiac diagnoses, including 19 with significant left to right shunts, who were undergoing routine cardiac catheterization (cath). On admission, patients were graded for CHF according to the following modified NYHA classification: I=No symptoms; II=Slight limitation of activity (dyspnea on exertion, diaphoresis with feeds); III=Marked limitation with prolonged feeding times (in infants) or failure to thrive, moderate to marked tachypnea and diaphoresis with activity; IV=Symptomatic at rest. They were routinely sedated for cath and the PNE sample was withdrawn from the femoral venous sheath after the patient was either fully asleep, awake but quiet, or when the HR and BP were at their baseline. Pulmonic to systemic blood flow (Qp/Qs) was determined by the Fick method. Results (*= P< 0.01):

TABLE A NYHA	#PT	PNE (mean±LSD) (pg/ml)
I	44	266.9±145.0
II	18	553.6±361.0 *
III/IV	8	1034.0±373.6 *

TABLE B Qp/Qs	#PT	PNE(mean±ISD) (pg/ml)
<1.8	51	336.1±242.6
≥1.8	19	689.7±450.4 *

We conclude that children with CHF have elevated PNE and these levels increase in proportion to the degree of failure (Table A). Patients with large left to right shunts had significantly higher PNE levels than those without or with small left to right shunts (Table B). PNE may be a useful indicator of the presence and severity of CHF in children.

AV NODE FUNCTION IN THE IMMATURE MAMMALIAN HEART

Jorge McCormack, M.D., Henry Gelband, M.D., F.A.C.C., Hui Xu, M.D., Adrienne Stolfi, Arthur S. Pickoff, M.D., F.A.C.C. University of Miami, Miami, FL.

Previous studies have suggested that the functional refractory period (FRP) of the neonatal AV node (AVN) is equal to or shorter than the FRP of the ventricle (V), providing little or no protection to the V against rapid atrial rates and allowing closely coupled atrial beats to fall within the "vulnerable" period of the V. We evaluated AVN function in 16 neonatal puppies (5-15 days) utilizing intracardiac His bundle recording and stimulation techniques. Though the effective refractory periods of the AVN and V were not different (141±18 msec, AVN; 140±14 msec, V), the AVN-FRP in the neonate was significantly longer than that of the V (178±17 msec, AVN; 163±14 msec, V, $p < 0.001$). During atrial extrastimulation, atrioventricular conduction delay was confined to the AVN (Type I response) in 15/16 neonates, while combined nodal and infranodal delay (Type II) was observed in 1/16. In none of the neonates were increases of more than 20 msec observed in A2H2 or H1H2 with any 10 msec decrease of A1A2. As another measure of AVN function, the paced HR resulting in AVN Wenckebach was determined and compared to the resting HR in the neonates and in a group of adults (n=10). The HR at which Wenckebach occurred in the neonates was 322±34 and in the adults 276±59. When divided by the resting HR for each group, comparable ratios were obtained for the neonates and adults (1.8±0.3, neonates; 2.1±0.3, adults). V arrhythmias were never induced in the neonate during atrial pacing. We conclude that, contrary to previous reports, the neonatal AVN-FRP is longer than the V-FRP. Furthermore, the degree of protection offered by the neonatal AVN to the V against rapid atrial rates is comparable to that observed in the adult.

SHUNT SIZE AND LONG-TERM PATENCY IN SURGICALLY CREATED VENTRICULAR SEPTAL DEFECTS IN LABORATORY RATS

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Although pulmonary vascular disease due to congenital heart defects has long been recognized as an important problem, little is understood of the mechanisms by which it develops because of the paucity of animal models which permit systematic study. In order to investigate the pathogenesis of Eisenmenger Syndrome in an inbred animal suitable for long-term studies, we have developed a technique for producing a VSD in the laboratory rat which consistently results in large pulmonary/systemic flows (Qp/Qs) for as long as 20 weeks postoperatively.

This technique is described as follows. Adult rats are anesthetized, a right thoracotomy performed, and a purse-string placed in the RV wall of the beating heart. By means of a specially constructed device, a 5 mm polyethylene grommet with an internal diameter of 1.1 mm and a flange at one end is inserted through the RV wall and ventricular septum. When the device is withdrawn, the grommet remains lodged in the septum. Of the operative survivors, less than 20% succumb after the first 24 hrs.

To assess shunt patency, 28 rats have been electively sacrificed. Fifteen (54%) had large left-to-right (L-R) shunts (Qp/Qs > 2); 1 had a Qp/Qs < 2; the remainder had no shunt. In those with shunts, Qp/Qs (mean + SEM) by oximetry was 4.8+.5 overall: 4.6 at 1-2 wks (9 rats), 4.9 at 6-9 wks (5), and 5.4 at 20 wks (2). Because streaming may result in an overestimation of pulmonary flow by oximetry, Qp/Qs was also determined in 8 rats by counting activity in the lungs following injection of radioactive microspheres into the left atrium. Average microsphere Qp/Qs was 2.3 + .3 overall: 2.7 at 1 wk (3 rats), 2.1 at 6 wks (3), and 2.2 at 20 wks (2).

These data indicate that it is possible to create a VSD in the rat with shunts consistently of a magnitude which are clinically significant. The laboratory rat may, therefore, prove a useful model for the study of Eisenmenger Syndrome as well as other sequelae of chronic L-R shunts.

UNEXPLAINED SYNCOPE IN CHILDREN: COST-EFFECTIVE WORKUP?

Douglas S. Moodie, M.D., F.A.C.C., Matthew Passalacqua, B.A., Richard Sterba, M.D., F.A.C.C., A. David Rothner, M.D., Gerald Erenberg, M.D., Robert P. Cruse, D.O. Cleveland Clinic Foundation, Cleveland, OH

The cost-effectiveness of the diagnostic workup of syncope in children has not been evaluated. We studied 73 pediatric patients (pts) with documented syncope. There were 34 males and 39 females who ranged in age from 2 1/2 to 20 yrs (mean age 14 yrs) at presentation. The following table lists neurologic and cardiologic tests performed and how many of these tests were normal.

Test	# Performed	Normal
Neurologic consultation	65	64
Electroencephalogram	64	63
CAT scan	37	36
Cardiac consultation	46	44
EKG	68	64
X-ray	43	43
Echo	43	39
Stress test	21	21
Holter	43	43
EPS	7	6

Of the 73 pts, only 3 (4%) had serious abnormalities which could account for their syncope. The total cost for the diagnostic tests in these 73 pts was $75,494. Six diagnostic tests were performed per pt. Twenty-nine pts were also hospitalized giving an average cost for the total workup in the 73 pts of $2,973 per pt. Follow-up ranged from 2 wks to 7 yrs (mean 2 yrs) on 50 pts (69%). Only 9 pts still experienced syncope and in 7 the syncope was less. The need for a more goal directed and cost-effective approach to pediatric pts with syncope of unknown origin is neccesary, although at follow-up most pts' syncope had disappeared or was less.

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LATE ELECTROPHYSIOLOGIC EFFECTS OF EXPERIMENTAL RIGHT VENTRICULOTOMY

Jeffrey P. Moak, MD, Arthur Garson, Jr., M.D., F.A.C.C., Texas Children's Hospital, Houston, Texas.

Right ventriculotomy (Ven), required for the repair of congenital heart defects, has been implicated as a substrate for ventricular arrhythmias (VA) and conduction disturbances (CD) following cardiac surgery. RVCD have important late implications. In the presence of central CRBB, the development of atherosclerotic LBBB would cause complete AVB. Our purpose was to study the electrophysiologic (EP) effects of Ven performed early in life. Six beagle puppies underwent Ven at 8 weeks of age; holter and clinical EP study at 14 mo., followed by microelectrode study (ME). The RV preparation consisted of the RV septum and attached free wall. During superfusion with Tyrode's solution and pacing the proximal RBB at 500 msec, 200-250 ME impalements of the endocardial surface were made. Six beagle puppies, with all except Ven, were the control group (C). Impalements were grouped into 5 regions: outflow septum (OS), inflow septum (IS), outflow free wall (OFW), inflow free wall (IFW), and Ven region (VR). We found: 1) No spontaneous or induced VA or CD were detected in vivo in the Ven or C. 2) In the C, regional differences in action potential (AP) characteristics were observed. AP amplitude was > in the FW. OFW-119 +/- 2 vs OS-113 +/- 3mv, P<.01; IFW-118 +/- 3 vs IS-108 +/- 3mv, P<.01. V max was > in the FW. OFW-527 +/- 29 vs OS-391 +/- 38 V/sec P<.01; IFW-500 +/- 32 vs IS-262 +/- 31 V/sec, P<.01. APD 100 was > in the FW. OFW-220 +/- 18 vs OS-202 +/- 15 msec, P<.01; IFW-223 +/- 28 vs IS-200 +/- 15 msec, p<.01. Similar differences were observed in the Ven. 3) No cellular activity could be recorded from 51% of impalements within the Ven scar, yet NS differences in AP characteristics were observed for those cells successfully impaled surrounding the Ven. 4) Within the Ven scar, delay and conduction block in local areas (0.5-1.0mm) were observed. 5) Despite these abnormalities, there was no delay of regional activation of the VR or OFW. In conclusion, no spontaneous or inducible clinical VA occurred if Ven healed at low RV pressure. Ven had no effect on AP characteristics. No RBB occurred with isolated Ven in the OFW. Our results suggest "peripheral" RBB that develops following VSD repair may be more "central" in origin.

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CARDIAC ARRHYTHMIA AS A MECHANISM OF SYNCOPE IN CHILDREN WITH NORMAL HEARTS.

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Fourteen children ages 4-19 years (mean 13.6 yrs) presented with recurrent syncope. A complete physical examination and cardiac catheterization in all patients showed a structurally normal heart. At the time of referral 5/16 were treated for seizures despite normal electroencephalogram. All patients underwent 24-hour ambulatory electrocardiogram, exercise testing, and invasive electrophysiologic study. Cardiac arrhythmia was identified as a cause of syncope in all, atrio-ventricular (A-V) block in 6/14, ventricular tachycardia (V.T.) in 4/14, sinus node dysfunction in 2/14 and supraventricular dysrhythmia in 2/14. Syncope occurred with exercise in 5 patients; 4 of these had exercise induced ventricular tachycardia and 1 had A-V block with exercise. Out of 6 patients with A-V block only 2 required pacing. Of 4 patients with V.T. effective drugs included beta blocking drugs in all in combination with dilantin or Procainamide in 3/4. These patients have been followed for a period of 3-45 months with a mean follow-up of 22 months. During this follow-up period syncope recurred in 3 patients; 2/3 recurrences occurred when drug levels were subtherapeutic. Conclusions: These studies demonstrate that cardiac arrhythmia is not an uncommon cause of recurrent syncope in children with structually normal hearts and that appropriate antiarrhythmic drugs or pacing prevent recurrent syncope effectively.

ELECTROPHYSIOLOGIC ASSESSMENT OF SINUS NODE DYSFUNCTION IN POSTOP PEDIATRIC PATIENTS UTILIZING COMBINED AUTONOMIC BLOCKADE

Barry Marcus, M.D., Paul C. Gillette, M.D., FACC, Richard T. Smith, M.D., Jeffrey P. Moak, M.D., Alex Zinner, Arthur Garson, Jr. M.D., FACC; Baylor College of Medicine and Texas Children's Hospital, Houston, Texas.

Sinus node dysfunction (SND) is a recognized problem following surgery for certain congenital heart defects. To distinguish disordered autonomic regulation from intrinsic sinus node disease, 7 postop (PO) pts with SND (5 Mustard, 1 Tetralogy of Fallot (Tet), 1 Fontan) underwent electrophysiology study (EPS) of SN function at rest and during combined autonomic blockade (CAB) utilizing propranolol (0.2 mg/kg IV) and atropine (0.04 mg/kg IV). During CAB, intrinsic heart rate (IHR), intrinsic corrected sinus node recovery time (INT-CNSRT) and intrinsic sinoatrial conduction time (INT-SACT) were measured. These results were compared with age-matched controls from our lab. Normal (n=7, mean age 9 yrs) IHR=128 ± 24, INT-CSNRT=135 ± 40 msec, INT-SACT=86 ± 19 msec.

Among pts PO Mustard (n=5, mean age 13 yrs, mean yrs PO 11), 5/5 had abnormal rest EPS, all had prolonged INT-SACT, but 3/5 had normal IHR. The pt PO Tet (age 20 yrs, PO 14 yrs) had mildly abnormal rest and intrinsic SN EPS. The pt PO Fontan (age 16 yrs, PO 1.5 yrs) had sinus rhythm at rest but left atrial rhythm during CAB. Conclusions: Different aspects of SND may be expressed during resting EPS vs EPS utilizing CAB suggesting that the clinical manifestations of SND can vary with the prevailing state of autonomic tone. It is possible that some of the SND seen in postop pts may be on the basis of disordered autonomic regulation in concert with intrinsic dysfunction.

DOES RESPONSE TO I.V. AMIODARONE AT ELECTROPHYSIOLOGIC STUDY PREDICT CLINICAL RESPONSE TO ORAL THERAPY IN CHILDREN WITH SVT? Ashok V. Mehta, MD, FACC; G.R. Sanchez, MD, S. Brickley, CCPT; A. O'Riordan, MD; R. Donner, MD. St. Christopher's Hosp. for Children, Phila., PA.

Correlation between response to I.V. amiodarone (AM) at electrophysiologic study (EPS) and oral AM therapy in children with supraventricular tachycardia (SVT) is not reported. The reported long-term side effects are variable. We treated with AM 12 children, age 8 mo-21 yrs (median 10 yrs) with SVT refractory to conventional therapy.

Of 10 pts who were given I.V. AM (5 mg/kg) at EPS over 5 minutes, 2 with W-P-W syndrome and 1 intraatrial SVT had inducible SVT at 30 & 45 min but none had SVT at 60 min and all were controlled on oral AM; 1 with intraatrial and 1 fast-slow type SVT had persistent SVT at 30 & 60 min and on oral AM; 3 with ectopic atrial SVT had suppression of SVT at 45-60 min post-AM and on oral AM; 2 had persistent atrial fibrillation and oral AM was not started. None had any side effects with I.V. AM therapy. On oral AM trial only, 1 ectopic SVT was well controlled and 1 WPW syndrome had recurrence on a large dose.

Nine pts were maintained on AM for 3 to 40 (median 18) months. During follow-up, complications were: 1 reversible hypothyroidism after discontinuing AM, 1 chemical hypothyroidism and mild hypertension, 1 sudden death, 2 transient pruritic skin rash, 1 transient personality change, and 3 corneal opacities.

We conclude that 1) for SVT in children, EPS 45-60 min post I.V. amiodarone is helpful in predicting the clinical response to oral AM (8/8 pts) 2) I.V. and oral AM is useful in suppressing ectopic atrial SVT (4/4 pts), and 3) AM is associated with significant side effects.

ELECTROPHYSIOLOGIC CHARACTERISTICS OF YOUNG PATIENTS WITH ACCESSORY PATHWAYS AND SUPRAVENTRICULAR TACHYCARDIA.

Barbara Deal, M.D.; Daniel Scagliotti, M.D.; Darrell Prechel, B.S.; Jose Gallastegui, M.D., FACC; and Robert Hariman, M.D., FACC; University of Illinois, Chicago, Illinois.

To evaluate the characteristics of arrhythmias in young pts. with accessory pathways, we performed electrophysiologic studies (EPS) in 17 pts. without structural heart disease presenting with recurrent symptomatic supraventricular tachycardia (SVT) involving accessory pathways. The mean age of the pts. was 16.7 yrs. (range 6-21 yrs.). Tachycardias identified at EPS were orthodromic SVT (15 pts.), antidromic SVT (5 pts.), and atrial fibrillation (AF) (6 pts.). All pts. with AF also had either orthodromic SVT (4 pts.) or both orthodromic and antidromic SVT (2 pts.). During chronic drug studies, a mean of 3.5 drugs/pt. were tested. Drugs successful in preventing induction of sustained SVT were identified in 10/11 pts. without AF. In contrast, induction of AF and SVT could be prevented in only 2/6 pts. with AF. Antegrade refractory periods of the accessory pathway (range 220-400 msec.) did not correlate with either age or the presence of AF. During a mean follow-up period of 3.4 yrs., chronic anti-arrhythmic therapy based on EPS has been successful in preventing sustained SVT in 10/13 pts.; 4 pts. with AF underwent surgery. We conclude that in young pts. with accessory pathways and SVT: (1) EPS successfully identifies effective drug therapy in the majority of pts. without AF; (2) AF is not uncommon in this age group, and is frequently associated with reciprocating SVT, suggesting that the accessory pathway and reciprocating SVT may be implicated in the generation of AF; and (3) surgery is frequently necessary in young pts. with AF.

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CATHETER ABLATION OF ECTOPIC ATRIAL OR JUNCTIONAL TACHYCARDIA FOCI

Jesse C. Davis, M.D., Melvin M. Scheinman, M.D., F.A.C.C., Michael A. Ruder, M.D., and Jerry C. Griffin, M.D., F.A.C.C., University of California, San Francisco, CA.

Five patients (pts) (ages 17-42 yrs) with incessant or persistent atrial or junctional tachycardia resistant to drug therapy for 14±7 yrs underwent programmed electrical stimulation, endocardial mapping and attempted catheter ablation of arrhythmic foci. One had cardiomyopathy, 2 developed tachycardia following cardiac surgery and 2 had no cardiac disease. The tachycardia cycle length was 390±72 msec and was irregular in 3 of 5 pts. Transient slowing of tachycardia occurred in 2 following overdrive pacing but neither overdrive nor premature atrial or ventricular stimulation provoked or terminated the tachycardia. Tachycardia originated in: the right atrial appendage (RAA) in one, the posterior septum (PS) in 2, the atrioventricular junction (AVJ) in 2. One or more direct-current shocks were delivered from an electrode closest to the earliest area of endocardial activation to a patch on the chest wall. The mean energy used and the peak CPK MB units were 490±175J, 37±29 U/L, respectively. Two pts with AVJ tachycardia required chronic cardiac pacing. After a follow-up of 7±6 mos, surgical amputation of the RAA was necessary because of recurrent atrial tachycardia in one, one pt with PS tachycardia developed atrial flutter and required quinidine, while the others remain free of tachycardia without drug therapy. In all pts, the mechanism of tachycardia appeared to be due to enhanced automaticity. Catheter ablation of right atrial foci is particularly attractive since AV conduction is preserved. Arrhythmia control is possible in those with incessant AVJ tachycardia but sacrifice of atrioventricular conduction is required.

IN VITRO ANALYSIS OF EMBOLIC POTENTIAL OF LASER IRRADIATION OF CALCIFIED CARDIOVASCULAR TISSUES.

Jeffrey M. Isner, M.D., F.A.C.C., Roberta F. Donaldson, B.S., Richard H. Clarke, Ph.D., Tufts-New England Medical Center, Boston, MA.

The embolic potential of calcified cardiovascular tissues subjected to laser (L) irradiation has important implications for the extent to which L irradiation can be applied indiscriminately to all varieties of atherosclerotic plaque. A series of in vitro experiments was therefore designed to evaluate this issue, utilizing 5-mm. segments of heavily calcified human coronary arteries (CAs) obtained fresh at the time of necropsy, in which the lumina were totally or sub-totally occluded by atherosclerotic plaque (n=24); and heavily calcified aortic valve (AV) leaflets (n=13) excised at AV replacement. L irradiation was delivered in the continuous mode from an argon laser (484-514 nm) to tissue samples immersed in saline within a quartz cell. Radiographs were used to document the extent of calcific deposits pre-and post-L irradiation. Power was varied between 4 and 14 watts; exposure was protracted (10-15 min) in order to maximize embolic potential. Post-L-irradiated solution was examined by gross inspection; by radiographic analysis of graded filtrates; and by microscopic examination of spun sediments of graded filtrate. Results: in each case, the pre-and post-L radiographs documented at least partial ablation of calcified lesion; ablation was typically more complete for calcified CA segments than for calcified AV leaflets. In no case, however, did gross inspection, radiographic, or microscopic analysis of graded filtrates disclose evidence of particulate, including calcified, particulate material. Conclusion: these experiments indicate that vaporization of calcified cardiovascular lesions induced by L irradiation proceeds from solid to gas phase without generation of particulate debris, suggesting that in vivo L ablation of such lesions is unlikely to be complicated by distal particulate embolization.

ANALYSIS OF VAPOR-PHASE PHOTOPRODUCTS RELEASED DURING EXCIMER LASER PHOTOABLATION OF CARDIOVASCULAR TISSUES.

Richard H. Clarke, Ph.D., Jeffrey M. Isner, M.D., F.A.C.C., Tufts-New England Medical Center, Boston, MA

Analysis of photoproducts generated during continuous wave (CW) laser irradiation of cardiovascular tissues has disclosed vapor-phase products indicative of a thermal mechanism of laser photoablation; corresponding histologic examination of the irradiated tissues has disclosed signs of thermal injury. Excimer laser (ExL) irradiation typically results in no pathologic evidence of thermal injury; photoproducts liberated during ExL irradiation, however, have not been previously described. Accordingly, gas chromatographic (GC) analysis was performed of vapor-phase photoproducts released during ExL irradiation of atherosclerotic coronary segments and myocardium in air (n=14), and blood (n=8). In air, the principal ExL wavelengths (193, 248, 308, 351 nm) were delivered to tissue samples through the wall of a quartz cell, using 10 to 100 mJ/pulse. Gas-phase photoproducts were collected by withdrawing 1-5 cc gas samples into a syringe through a rubber septum at the top of the cell. In blood, 351 nm was delivered via an optical fiber to the sample placed in the cell under a 3-cm column of blood, using 14 mJ/pulse; the fiber tip was positioned 1-2 mm above the tissue surface. In air, dominant photoproducts identified in order of elution from the GC column were: methane, acetylene, ethylene, ethane; propyne, allene, propylene, and propane; and butene. When a fiberoptic was used to deliver 351 nm ExL emission, a similar GC spectral distribution was noted. These photoproducts are indistinguishable from those previously identified during CW laser experiments. These results suggest that the mechanism by which ExL effects photoablation is not essentially different from the mechanism involved in CW laser irradiation, despite the observed differences in light microscopic findings.

A NEW BALLOON CATHETER AND PRESSURE GENERATING DEVICE FOR R - WAVE - TRIGGERED CORONARY DILATATION WITH DIASTOLIC FLOW MAINTENANCE.

Adolf Kuhl, M.D., Paul R. Lichtlen, M.D., F.A.C.C. and Otto Anna, Ph.D., Medical School Hannover, Federal Republic of Germany.

A new dilatation system is developed allowing systolic inflation and diastolic deflation of the balloon. Additionally, during dilatation coronary flow is maintained without external perfusion. The dynamic data of the catheter measured by piezoelectric pressure transducer are: pressure generator pulse rise time = 2 ms; peak pressure = 16 atm.; balloon inflation time = 40 ms; deflation time = 60 ms; pressure drop = 2 atm.; burst pressure = 12 atm.; balloon diameter = 3.0 mm at 8 atm.. The frequency response permits transmission of 20 Hz; resonance frequency is 9 Hz (alternating pressure). We studied 8 dogs (thoracotomy, magnetic flowmeter LAD/RCX, angiography) to prove continuous flow during dilatation. When the inflation time of the balloon is up to 80% of the RR - interval flow decreases only to about 50% of the prior existing flow level (balloon deflated). Triggering during systole reveals no significant decrease of flow. The transfer function of the dynamic dilatation system enables alternating of the balloon diameter induced by defined pressure steps. Additionally, sinus wave shaped pressure profiles of up to 40 Hz can be superimposed to the basic inflation tone. From these data it is concluded that this new dilatation procedure may become better controlled, more effective and safer in treatment of various types of stenosis in coronary artery disease.

ELECTROPHYSIOLOGIC CHARACTERISTICS OF CENTENARIANS: EVALUATION BY RESTING AND AMBULATORY ECG

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Uncertainty continues regarding the incidence and nature of electrophysiologic disturbances associated with aging. Therefore, we performed resting (20 pts) and ambulatory (AM) (10 pts) ECG in 20 individuals documented to be 100 years of age or greater. Only 6 of the subjects had any symptoms or signs compatible with heart disease or hypertension (mild in all), however, 8 were taking digitalis and 9 diuretics. A normal rest ECG was obtained in only 4 subjects. Heart rate ranged from 56-86 and 29-114 beat/min by rest and AM ECG respectively. The PR interval was $\geq$ 200 msec in 12/18 subjects (mean 210). Left ventricular hypertrophy, left anterior hemiblock, right bundle branch block and left bundle branch block were found in 3/20, 7/20, 1/20 and 4/20 respectively. The QT interval corrected for heart rate was prolonged in 15/18. Two subjects manifested atrial fibrillation. Of the individuals continuously monitored, supraventricular tachycardia manifested as runs of 3 or more beats was present in 8/10 and isolated premature atrial beats were present in 10/10. During AM 9/10 had isolated premature ventricular complexes, 6/10 had ventricular couplets, and 3/10 had ventricular tachycardia. Thus, ECG is typically abnormal in centenarians even in the absence of overt heart disease. Significant abnormalities of cardiac rhythm and conduction appear to accompany, but not to prohibit, advanced age.

PROGNOSIS OF PATIENTS WITH THE MARFAN SYNDROME DIAGNOSED AFTER AGE 32.

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Most patients with the Marfan syndrome (MS) die of cardiovascular (CV) complications; the mean age at death is said to be 32 years. We have identified 28 patients (15 males, 13 females) in whom MS was first diagnosed after age 32 (mean age, 46; range, 32-72) and have evaluated their CV system. Each had at least 2 of the 4 major diagnostic criteria for MS--family history, long-limbed habitus, dislocated lenses, and aortic disease. At the initial diagnosis, only 8 patients were referred for cardiac symptoms, but 23 had signs of CV disease. Twenty-seven patients (96%) were followed for a mean of 70 months (range, 1-239). Nine died (7 from CV disease and 2 from cancer). Eleven patients had a total of 15 operations; 4 had 2 operations each. Ten operations were for ascending aortic aneurysms; 5 were for aortic dissection--3 in ascending aorta and 2 in previously operated aortas. Only 1 patient required mitral valve replacement for mitral insufficiency. A total of 14 patients (52%) had CV events during the follow-up. These occurred in 11 of 15 patients with and in only 2 of 10 without clinical evidence of aortic insufficiency. Among 13 patients with echocardiographic dilated aortas, 7 had CV events; none of 4 patients with normal aortas had CV events. Thus, patients first diagnosed to have MS after age 32 are rare. They are susceptible to a very high incidence of CV complications, especially when aortic involvement is present. Significant mitral insufficiency is uncommon.

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Pharmacology—Basic

CESIUM-INDUCED LATE-COUPLED, TRIGGERED ACTION POTENTIALS IN PURKINJE FIBERS

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Cs induces early afterdepolarizations (EAD) and multiform ventricular tachyarrhythmias in dogs resembling "Torsades de Pointes". Because hypokalemia and bradycardia often predispose Torsades de Pointes, we superfused ventricular tissues from 35 guinea pigs with low-K (2.0 mM) Tyrode solution, and stimulated at 0.2 Hz. Maximum diastolic potentials hyperpolarized to -96+2mV as measured by standard microelectrode techniques. Cs (3.6mM) did not induce EADs in hyperpolarized cells at low K_o, but triggered (T) action potentials (APs) occurred after intervals of 50-200 msec of stable diastolic potential with no interposed EADs. Stimulated APs were followed by one or more TAPs in which the rapid upstrokes appeared without slow depolarizing prepotentials. TAPs were associated with a progressively prolonged plateaus and were reversibly supressed by increasing the stimulus frequency and shortening of the plateau. Both fast and slow channel integrity were necessary for TAPs, because low concentrations of inhibitors of either channel (TTX:2x10-8M; D-600:1x10-6M) selectively eliminated TAPs. Automaticity as a mechanism for TAPs is unlikely, because Cs inhibits pacemaker currents. Exploration throughout the small preparation failed to show phase 4 depolarization. Reentry could be ruled out because late TAPs occurred in small Purkinje strands even when conduction was prevented by field stimulation. Cs-induced EADs have been related to inhibition of repolarizing currents, however, the mechanism of late TAPs remains to be elucidated.

FACILITATED ABSORPTION OF INTRAMUSCULAR (i.m.) HUMAN rt-PA WITH METHYLAMINE -- A REMARKABLY NON-TOXIC AGENT

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We previously induced coronary thrombolysis with i.m. rt-PA with absorption facilitated by hydroxylamine (HA) in the injectate and electrical field stimulation (EFS). However, HA can induce significant methemoglobinemia, and transient hypotension and tachycardia. To obviate such potential effects, in this study we characterized factors contributing to enhancement of absorption of rt-PA and the potential utility and toxicity of analogs of HA in 64 rabbits. Absorption was measured after i.m. injections of 2 to 3 mg of concentrated t-PA (50 mg/ml) in solutions with HA (2.6 to 175 mg, n = 17), in hypertonic media without HA (0.63 M NaCl, n = 2), with vasodilators (.01 M adenosine or .09 M hydralazine, n = 4), with analogs of HA including several primary amines (n = 36), or with t-PA alone (n = 5). One agent, methylamine, was particularly salutary. Methylamine HCl (0.63 M) plus EFS elicited blood levels of rt-PA within 5 min after i.m. injection of rt-PA, with functional and immunologic activity similar to that achieved with HA (129 vs 137 ng/ml/mg rt-PA). However, in contrast to the case with HA, neither methemoglobinemia nor hemodynamic derangements occurred, oxygen saturation remained unchanged, and only modest local inflammation and interstitial hemorrhage were evident microscopically in the injection site after 48 hr. Vasodilators, hypertonic media, reduced amounts of HA, or rt-PA alone led to much lower blood levels of rt-PA (14, 65, 46, and 4 ng/ml/mg rt-PA respectively). Thus, enhancement of absorption with methylamine leads to effective blood levels of rt-PA after i.m. injection without toxic effects potentially associated with hydroxylamine.

COMPARATIVE EFFECTS OF NITROGLYCERIN AND DILTIAZEM ON REGRESSED, NEWLY DEVELOPED CORONARY COLLATERALS IN CONSCIOUS DOGS.

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We evaluated acute effects of nitroglycerin (NTG) and diltiazem (DTZ) on collateral blood flow (CBF) and regional myocardial function in collateral zone during 2 min coronary occlusions (CO). Studies were conducted in 8 awake unsedated dogs instrumented for measurement of left circumflex coronary artery (LCCA) flow, segment lengths in areas perfused by LCCA and left anterior descending artery (LAD). Pneumatic occluders were placed around each vessel. Brief, repeated LCCA CO induced collaterals sufficient for resting metabolic demands in the region supplied by the LCCA. One week following cessation of repeated LCCA CO, 2 min LCCA (4 dogs) or LAD (4 dogs) CO with and without drug pretreatment were performed on separate days. CBF from the LCCA to the occluded LAD area was measured as the stepwise decrease in LCCA flow upon release of LAD CO. During control CO, ischemic segment shortening (%ΔL) deteriorated to 33±9 (SEM)% of preocclusion resting values. Following release of LCCA CO, blood flow debt repayment (BFDR) was 166±53%. CBF during LAD CO was 20±5% of resting LCCA flow. These responses were not altered by DTZ (50 μg/kg, iv), but NTG (5 μg/kg, iv) improved %ΔL (58±14%, $p<.05$) associated with decrease in BFDR (74±26%, $p<.05$) and increase in CBF (30±8%, $p<.05$). Thus, NTG produced greater effects than DTZ in increasing CBF and regional myocardial function in the collateral dependent zone when effects of each drug on systemic circulation were minimized by pretreatment with small doses.

DEMONSTRATION OF IMPAIRED CHOLINERGIC VASODILATION IN THE ATHEROSCLEROTIC RABBIT IN VIVO

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Endothelium-dependent cholinergic relaxation in vitro is impaired in large arteries from patients or animals with atherosclerosis. To assess the significance of this impairment, we compared vasodilator effects of acetylcholine (Ach) and nitroprusside (Np), an endothelium-independent agent, in control rabbits (C;n=9) and in rabbits fed a 1% cholesterol diet for 10 weeks (A;n=6). After 10 weeks, plasma cholesterol in C and A averaged 58±6 and 2,100±110 mg/dl ($P<0.01$). The hindlimb of the rabbits was perfused during pento-barbital anesthesia via an extracorporeal loop at a constant flow of 5 ml/min, which produced femoral arterial perfusion pressures of 71±3 (SE) and 74±2 mm Hg in A and C ($p>0.5$). Effects of Ach and Np bolus injections on hindlimb vascular resistance were determined, and dose-response curves for the two agents were constructed. Relative potencies were assessed by calculating ratios (R) of peak vasodilator responses for the two agents. The R for 0.2mg Ach/5.0 mg Np averaged 1.46±0.18 for C, and 0.75±0.18 for A ($p<.01$). The R for 2.0mg Ach/50.0 mg Np averaged 0.96±0.08 for C and 0.56±0.11 for A ($p<0.01$). Thus, rabbits with hypercholesterolemia exhibited a significantly depressed endothelium-dependent cholinergic relaxation compared to relaxation evoked by nitroprusside. Since total vascular resistance is determined predominantly by arterioles, the results suggest that hypercholesterolemia may affect endothelium-dependent relaxation at the level of the resistance vasculature.

ENHANCED SALVAGE OF REPERFUSED MYOCARDIUM BY DILTIAZEM ADMINISTERED PRIOR TO CORONARY THROMBOLYSIS.

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To determine whether salvage of ischemic myocardium subjected to reperfusion after coronary thrombolysis can be enhanced significantly with calcium antagonists, coronary thrombi were induced in 27 dogs with an i.c. copper coil. Ten control dogs had persistent occlusion. Lysis was induced in 17 others with i.c. streptokinase (SK) 2 hr after occlusion. In 9 dogs given SK, diltiazem (15 μg/kg/min) was infused i.v. for 24 hr beginning 30 min before SK. Regional myocardial blood flow was quantified with microspheres during occlusion, 1 hr after thrombolysis, and 24 hr later. During occlusion flow averaged 0.10 ± .07 ml/min/g (mean ± S.D.) and did not differ among the three groups. Myocardial metabolism was assessed antemortum by carbon-11 palmitate positron tomography. Infarct size 24 hr after occlusion was quantified by assay of myocardial CK content and depletion. Although diltiazem did not enhance perfusion after thrombolysis (1.09 ± .48 without and 1.06 ± .51 with diltiazem), it enhanced salvage of myocardium. Thus, infarct size (percent of left ventricle) was greatest in controls (28 ± 11%), was diminished by thrombolysis alone (17 ± 10%, $p < .05$), and was markedly reduced by thrombolysis coupled with diltiazem (9 ± 7%) ($p < .05$ vs reperfusion alone). Increased ^{11}C-palmitate uptake in previously ischemic zones (56% compared with 40% of normal after reperfusion alone) was consistent with the results of myocardial CK analysis. Thus, diltiazem enhances myocardial salvage induced by coronary thrombolysis.

PREDOMINANCE OF SMALL VESSELS IN CORONARY CONSTRICTION DUE TO LEUKOTRIENE D_4.

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Leukotrienes (LT) are white cell products with powerful capacity to constrict coronary arteries (CA). Marked LT-induced contraction of isolated CA has led to the hypothesis that LT contribute to spasm in epicardial CA. However, the relative LT effects on small and large CA have not been demonstrated in vivo. We infused LTD_4, 2 mcg/min, into left anterior descending (LAD) CA of 6 open-chest pigs instrumented with LAD flowmeter and catheters in aorta (AO), left ventricle (LV) and proximal and distal LAD. Initially, LAD flow decreased from 43±3 to 13±2 ml/min (SE). Simultaneously measured pressure gradient from AO to distal LAD was unchanged from baseline, while small vessel flow resistance (distal LAD-LV diastolic pressure difference/LAD flow) increased from 1.4±0.2 to 4.6±0.6 mmHgxmin/ml ($p<0.001$). Thus, distal CA constriction was responsible for flow decrement induced by LTD_4. With continuing LTD_4 infusion, LAD flow "escaped" to 32±4 ml/min; peak reactive hyperemic flow remained blunted (62±8 ml/min vs. basal=151±22, $p<0.01$). Large CA resistance was only minimally increased (0.11±0.3 to 0.13±0.3 mmHgxmin/ml, $p=0.063$). Hence, continued exposure to LTD_4 can induce persistent decrement in CA flow reserve, mainly as a result of sustained small vessel constriction.

CORONARY VASODILATOR EFFECT OF VASOACTIVE INTESTINAL POLYPEPTIDE IN MAN.
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Vasoactive intestinal polypeptide (VIP), a probable neurotransmitter, is widely distributed in neurons, including those in heart and near coronary arteries. To investigate for a physiologic role of VIP in regulation of the coronary circulation in man, we studied vasodilation induced by VIP during intravenous infusion in 8 unanesthetized men (2 with and 6 without coronary stenoses) during diagnostic cardiac catheterization. VIP levels rose from 41±7 to 161±55 pg/ml ($\bar{x}$±SD) during infusion of 100 pmol/kg/h. Mean femoral artery pressure decreased 11% (106±19 to 94±19, p=.04), and heart rate increased 13% (70±11 to 79±10, p<.001). Mean pulmonary capillary wedge, right atrial, and pulmonary arterial pressures did not change. Cardiac output increased 21% (6.07±1.64 to 7.37±1.78 l/min p=.002). Coronary blood flow rose 30% (139±74 to 181±77 ml/min, p=.002). The 33% decrease in coronary vascular resistance (VR) during infusion (0.87±.45 to 0.55±.20 mmHg/ml/min., p=.011) was greater than (p<.025) the 20% decrease in pulmonary VR (104±64 to 83±46 dyne sec cm^{-5}, p=.022), but not significantly (p<.2) different than the 29% fall in systemic VR (1387±543 to 986±298 dyne sec cm^{-5}, p<.02). However, the decrease in coronary VR exceeded that of systemic VR in 6 of 8 patients. We conclude that: (1) VIP is a potent coronary vasodilator in man; (2) the coronary vascular bed appears to be more responsive than other vascular beds; and (3) these data are consistent with a possible physiological role for VIP in the regulation of coronary blood flow.

ENHANCED SALVAGE OF REPERFUSED, ISCHEMIC MYOCARDIUM BY α-ADRENERGIC BLOCKADE.
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We have previously shown that reperfusion of ischemic myocardium is accompanied by augmented α-adrenergic responsivity and a reversible increase of α_1-adrenergic receptor density. Furthermore, α_1-blockade immediately prior to reperfusion prevents intracellular calcium accumulation in jeopardized tissue. To determine whether α-blockade decreases irreversible injury as well, we studied chloralose anesthetized cats with or without phentolamine (1 mg/kg) or HEAT (.4 mg/kg) i.v. In cats subjected to proximal LAD coronary occlusion for 3 hr followed by 4 hr of reperfusion, the ratio of infarct area (determined by TTC staining) to risk region (determined with ^{99m}Tc-labeled microspheres immediately prior to reperfusion) was reduced by 29% (p<.02) by α-blockade 2 min before reperfusion (0.46 ± .04, n=7) compared with values in non-treated controls (0.65 ± .04, n=7). To determine whether this difference reflected net salvage or merely delay of necrosis, CK depletion was assayed at necropsy in myocardium from 17 additional animals. Following 3 hr of ischemia and 48 hr of reperfusion, the difference in infarct size was not significant (30 ± 7% in 9 treated cats compared with 38 ± 6% in 8 controls). However, α-blockade after less prolonged ischemia of 1 hr followed by reperfusion for 48 hr salvaged an additional 31% of jeopardized myocardium (infarct size = 22 ± 8%, n=6 compared with 32 ± 8%, n=6 with reperfusion without blockade). Thus, α-adrenergic blockade markedly enhances salvage of myocardium subjected to ischemia for 1 hr followed by reperfusion for 48 hr, suggesting that this intervention may be helpful clinically in the setting of thrombolysis.

CARDIAC GROWTH AND VENTRICULAR FUNCTION AFTER IMPLANTATION OF A GROWTH HORMONE SECRETING TUMOR: A NEW MODEL OF CARDIAC HYPERTROPHY
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To test the hypothesis that hypertrophy alters cardiac function, growth hormone secreting tumor cells (GH-3) or control media (C) was injected into 16 mature Wistar-Furth rats. Eight weeks after implantation, when body weight had increased an average of 47%, ventricular function was measured under anesthesia and analyzed by digital computer, and cardiac morphology was measured after sacrifice. Blood levels of growth hormone were 3854±2929 ng/ml in GH-3 rats and 176±261 ng/ml in C rats (p<0.01). Right and left ventricular weight increased an average of 41% and 36% respectively in GH-3 rats compared to C rats. When compared to C rats, GH-3 rats had significantly decreased heart rate (280±73 min^{-1} vs 219±39 min^{-1}, p<0.05), systolic, diastolic and mean arterial pressures (mean: 78.0±23.9 mmHg vs 51.8±7.5 mmHg, p<0.005) but no difference in LV end diastolic pressure (1.7±2.7 mmHg vs 3.7 + 3.5 mmHg, P=N.S.). GH-3 rats showed decreased indices of cardiac contractility (dp/dt) and relaxation (-dp/dt) compared to C; in response to graded doses of isoproterenol, these indices increased less in GH-3 than in C. We conclude that cardiac growth occurs in mature rats in response to GH excess and that cardiac performance and receptor responsiveness is decreased. This new model of cardiac growth offers excellent opportunities to study the physiology, morphology and biochemistry of hypertrophy.

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Coronary Artery Disease—Basic

MECHANISM OF DECREASED ISCHEMIA BY BETA-BLOCKADE DURING EXERCISE; DELETERIOUS EFFECT WITHOUT DRUG-INDUCED BRADYCARDIA.
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Beta-blockade has been shown to improve regional myocardial bloodflow (RMBF) and regional function during exercise-induced ischemia in conscious dogs. The role of reduced heart rate (HR) in this response was studied in 7 dogs chronically instrumented with an ameroid constrictor on the left circumflex coronary artery. RMBF (microspheres) and systolic wall thickening (%WT, sonomicrometry) were first measured during a control run in which HR increased from 107 ± 13 (SD) to 190 ± 14 beats per min, ischemic zone %WT decreased from 28.8 ± 10.6 to 12.5 ± 7.9% and subendocardial RMBF fell from 1.04 ± 10 to 0.66 ± 27 ml/min/g. An identical run was repeated after atenolol (0.3-1.0mg/kg,po), but during the run, atrial pacing was used to increase heart rate from 162 ± 11 to 192 ± 16 beats/min., the same level achieved in the control run. Regional function initially improved in the atenolol run compared to control running, but with pacing it deteriorated below that of the control run (%WT=6.8 ± 6.4, p<.05 compared to control run); RMBF decreased to 0.47 ± .22 (p <05).
These findings indicate that in the absence of drug-induced bradycardia negative inotropic effects and lowered blood pressure due to beta-blockade unfavorably influence regional flow and function; they further suggest that bradycardic drugs without negative inotropic properties should have even more favorable effects than beta blockade. It is concluded that the beneficial effect of beta-blockade on exercise-induced ischemia is due entirely to slowed heart rate, since with heart rate controlled a deleterious effect is produced.

SENSITIZATION OF REPERFUSED MYOCARDIUM TO SUBSEQUENT DECLINES IN CORONARY BLOOD FLOW. Erwin Schröder MD. Donald Laughlin MSEE, Robert Kieso MS, Michelle Hunt BS, Birgit Grimlund, Richard Kerber MD, FACC, U of Ia, Iowa City, Ia

In open-chest dogs, regional myocardial systolic thickening recovers within 30-60 mins of reperfusion after a 5 min episode of severe ischemia. We hypothesized that such reperfused myocardium is sensitized to subsequent declines in coronary blood flow, and that this would become evident by more pronounced regional contraction abnormalities at equivalent flow reductions 30 mins after complete coronary occlusion (CCO) vs. before CCO. We studied 9 open-chest dogs with stable heart rate (pacing), controlled arterial pressure and autonomic blockade. An external shunt was placed between the carotid artery and LAD coronary artery; an ultrasonic flowmeter allowed reproducible flow reductions. Myocardial perfusion (P) was measured by radiolabeled microspheres and normalized to the nonischemic wall. Regional systolic wall thickening (WTh) was measured by a new miniaturized M-mode echo (5 MHz) probe fixed to the epicardium by suction. Regional P and WTh were measured at rest and during two different levels of stable flow reduction (shunt constriction) before (control) and 30 mins after 5 min CCO (n=5). In a separate group of dogs (n=4) no intervening CCO was done. Results (*=p<.02, 30 mins vs. control) (mean values) (P=% of opposite nonischemic wall):

		Rest		Flow Reduction 1		Flow Reduction 2	
Group	%	Control	30'	Control	30'	Control	30'
No CCO	P	86	83	60	54	46	38
(n=4)	WTh	46	38	25	21	-4	0
5' CCO	P	85	86	74	72	54	50
(n=5)	WTh	43	37	31	21	3	-8*

Conclusion: Reperfused myocardium is sensitized to subsequent coronary flow reductions; equivalent declines in P produce more severe regional contraction abnormalities after a brief coronary occlusion.

IN VIVO ANGIOSCOPIC DEMONSTRATION OF THROMBUS AS A CAUSE OF CYCLIC FLOW VARIATION IN STENOSED CANINE CORONARY ARTERY.
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An episodic, spontaneous decrease interrupted by restorations of coronary blood flow is known to occur in an experimental setting of a stenosed canine coronary artery with endothelial damage at the site of narrowing. In this preparation we studied mechanism responsible for this phenomena. Transluminal coronary angioscopy of an antegrade approach using ultrathin flexible high resolution fiberoptic catheter as well as selective coronary angiography were applied for this purpose. Intimal abrasion by a biopsy brush and external ligation of the proximal site under angioscopic vision were done in the left circumflex coronary artery in anesthetized open chest canine preparation. In seven these preparations characterised by cyclic blood flow and pressure variation in association with electrocardiographic ST elevation, angioscopic images of the stenosed area of the inner wall were monitored on the video display terminal. Spongy thrombus obliterated the stenosed segment and angiographically total obstruction when the flow decreased, and perforated thrombus as well as angiographically subtotal obstruction when the flow restored were clearly visualized. Postmortem study confirmed that thrombus initially produced over the area of intimal damage gradually distended distally and proximally and obliterated the lumen. This data support the previous studies in posturating the important role of acute, dynamic platelets aggregation and thrombus for cyclic flow variation in these experimental setting as well as Prinzmetal angina in the clinical situation.

SYMPATHETIC CORONARY VASOCONSTRICTION DURING ACUTE RIGHT VENTRICULAR PRESSURE OVERLOAD.
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It has been suggested that right ventricular (RV) failure during acute pressure overload results from ischemia when coronary blood flow cannot increase adequately to meet increased RV metabolic needs. This study was performed to determine whether maximum coronary vasodilation is present when RV failure occurs. RV myocardial blood flow (MBF) was measured with microspheres during acute pulmonary artery constriction (PAC) with a chronically implanted hydraulic occluder to produce RV failure, as indicated by an increase in RV end-diastolic pressure to greater than 15 mm Hg, in 8 unanesthetized dogs. MBF increased from 1.24±0.21 during control conditions to 2.55±0.33 ml/min/g during PAO. This value was far less than the maximum MBF of 4.35±0.81 ml/min/g during coronary vasodilation with adenosine (1.0 mg/kg/min) during control conditions. However, infusion of adenosine during PAO did not significantly increase MBF. When alpha-adrenergic blockade was produced with prazosin (0.5 mg/kg i.v.), adenosine increased MBF during PAO to 4.30±0.54 ml/min/g, not significantly different from adenosine during control conditions. These data indicate that MBF was not maximal when RV failure occurred, and that adrenergic coronary vasoconstriction limited the increase in MBF during acute right ventricular pressure overload.

DOPPLER BLOOD FLOW VELOCITY CHANGES AS A SENSITIVE INDEX OF THE SEVERITY OF CORONARY STENOSIS.
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Assessment of the functional severity of a coronary stenosis (CS) in coronary artery disease is complex. Presently available techniques are inadequate to predict the severity of a stenosis <75% in cross sectional area (CSA). Changes in coronary blood flow velocity (V) immediately distal to an evolving thrombus have been used as an index of thrombus progression and appeared to predict the severity of CS. The circumflex coronary artery (LCX) of open-chested dogs was instrumented with a micrometer controlled hydraulic occluder and Doppler flow probes placed proximal and just distal to the occluder. The proximal Doppler measured coronary blood flow (CBF). Millar pressure catheters were placed in the aorta and the 1st distal LCX branch to measure pressure drop (PD) across the stenosis. Occluder inflation mimicked an eliptical eccentric stenosis and the reduction in CSA was determined by coronary casts. The results were:

Decrease in CSA(%)	21.4±1.8	50.5±4.8	73.5±7.7	88.8±2.9
Increase in V(%)†	111±6*	150±8*	199±13*	368±69*
CBF (ml/min)	31±7	31±7	31±7	28±7
PD (mmHg)	4±2	5±3	5±2	34±12*
Hyperemic Response (%)†	94±11	85±12	75±17	21±18*

† baseline = 100%; values are mean ±1 S.D.
* p< 0.01 when compared to respective control values.

Thus, distal velocity changes are a sensitive index of early CS unlike other hemodynamic parameters. This may be of value in the intraoperative evaluation of the physiological significance of angiographically demonstrated stenosis at coronary bypass surgery.

PAPAVERINE INDUCED INCREASED FLOW ENHANCES PERFORMANCE OF REGIONAL POST-ISCHEMIC MYOCARDIUM

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Persistent regional dysfunction following brief coronary occlusions is improved by dipyridamole which potentiates adenosine and increases coronary blood flow. To confirm that coronary flow, and not a unique adenosine effect, is the critical factor, we undertook this study using papaverine, a smooth muscle relaxer and phosphodiesterase inhibitor with no known action on adenosine. Six open-chest dogs were instrumented with an LV pressure transducer and pairs of sonomicrometer crystals in the risk and control regions. After baseline measurements, papaverine 1mg/min IV was infused for 10 min. Repeated 5 min occlusions of the LAD were performed with 10 min reflow x12 with a final 90 min recovery period. Papaverine was then reinfused 1mg/min IV x10 min. Flow was assessed by microspheres at baseline, end of recovery and during papaverine infusions. Function was determined by systolic shortening and the end-systolic pressure-length relationship (ESPLR). The linear ESPLR, defined by a slope and an intercept (the calculated length at an LV pressure of 70mmHg, L70) was obtained as LV pressure rose during brief occlusions of the aorta. Below are mean data from the risk region.

	Shortening (%)	L70 (mm)	Slope (mmHg/mm)	Flow (ml/min/gm)
Baseline	18.6	10.1	35	1.1
Papaverine	21.9*	10.1	42	1.6*
Recovery/Post Ischemia	6.7*	12.0*	32	1.3
Papaverine/Post Rec	13.6*	11.2*	38	2.2*

*P<.05 compared to value above.

Before ischemia papaverine increased shortening, associated with a 10% decrease in mean blood pressure, but did not affect the load-independent ESPLR. With repeated occlusions risk region systolic shortening was reduced despite normal levels of flow, and the ESPLR shifted to the right reflecting decreased performance. Following papaverine flow increased 70%, shortening increased and the ESPLR shifted to the left indicating improved performance compared to recovery.

Conclusion: The results indicate that dysfunction in post-ischemic myocardium can be improved by increasing flows to supernormal levels, independent of the mechanism of vasodilatation.

CORONARY VASCULAR PROSTACYCLIN SYNTHESIS IS INHIBITED WHEN CYCLIC FLOW VARIATIONS ARE ABOLISHED WITH ASPIRIN IN NARROWED CANINE CORONARY ARTERIES.

Juliet H. Ashton, Ph.D., William B. Campbell, Ph.D., James M. Schmitz, M.D., Anne Taylor, M.D., Suresh Raheja, M.D., L.M. Buja, M.D., F.A.C.C., James T. Willerson, M.D., F.A.C.C., Univ. of TX Hlth Sci Ctr, Dallas.

Previously, we reported that 1.1-4.6 mg/kg aspirin (ASA) eliminated cyclic flow variations (CFVs) in a canine model of coronary artery (CA) stenosis in 75% of dogs. A high dose of ASA (35 mg/kg) was no more effective than lower doses in abolishing CFVs. In this study, we determined whether the lower doses of ASA inhibit both platelet thromboxane A_2 (TxA_2) and vascular prostacyclin (PGI_2) synthesis while also abolishing CFVs. CFVs, characterized by repetitive cycles of declining CA blood flow interrupted by spontaneous increases in flow were established, and then abolished with ASA (1.1-9.2 mg/kg) in stenosed left anterior descending CA (LAD STEN) in 6 dogs. CFVs were also established in a separate group of 6 dogs (NoASA) for 1 hour. LAD STEN and normal circumflex (CIRC) vessel segments were incubated at 22°C with vehicle alone (V) or arachidonic acid (AA). TxB_2 and 6-keto-$PGF_{1\alpha}$, inactive metabolites of TxA_2 and PGI_2, were measured by RIA in the incubation media. Values below are expressed as mean ± SEM, pg/mg tissue. *p<0.05 significantly different from V in the same treatment group.

	CIRC		LAD STEN			
	6-K-$PGF_{1\alpha}$		TxB_2		6-K-$PGF_{1\alpha}$	
AA	NoASA	ASA	NoASA	ASA	NoASA	ASA
V	76±9	56±22	38±6	7±4	81±8	58±12
10^{-6}M	201±19*	42±7	122±28*	19±9	117±11*	61±14
10^{-5}M	350±30*	54±5	142±27*	49±5*	125±12*	53±8

Thus, PGI_2 synthesis is inhibited and TxA_2 synthesis is markedly impaired by relatively low ASA concentrations that also eliminate CFVs, suggesting that TxA_2 is an important mediator of CFVs in this experimental model.

MYOCARDIAL ISCHEMIA ATTENUATES CORONARY CONSTRICTION DUE TO A THROMBOXANE A_2 ANALOG.

Francisco RM Laurindo, M.D., David Ezra, M.D., John Czaja, Giora Feuerstein, M.D., and Robert E Goldstein, M.D., F.A.C.C., USUHS, Bethesda,MD.

Thromboxane A_2 (TXA_2) is synthesized during acute myocardial ischemia and has been thought to exert adverse coronary constrictor effects. However, consequences of TXA_2 exposure to regionally ischemic in situ hearts have not been explored. We infused U-46619, [(5Z,9α, 11α,13E,15S)-11,9-(Epoxymethano)prosta-5,13-dien-1-oic acid] a stable TXA_2 analog, into left anterior descending coronary artery (CA) of 14 open-chest pigs, as 1,3 and 10 mcg boluses, each dose before and during 10 min myocardial ischemia caused by a proximal subtotal CA stenosis (snare). Coronary flow (CBF, flowmeter), aortic pressure, regional contraction and distal CA pressure (n=6) were monitored. CBF(ml/min, mean±SE):

		1mcg(n=5)	3mcg(n=7)	10mcg(n=10)
CONTROL	BASELINE-	64±8	63±6	55±4
	U-46619 -	40±10**	38±3*	25±2*
ISCHEMIA	BASELINE-	20±3*	24±4*	21±3*
	U-46619 -	20±3	24±4	20±3

*p<0.01 or **p<0.05 vs. control baseline (ANOVA)

Baseline pressure differences from aorta to distal CA (control = 0 ± 0 and ischemia = 46 ± 6 mmHg) were not modified by U-46619. Thus, constriction of small coronary vessels due to TXA_2 is remarkably attenuated or abolished during ischemia. Our results suggest that small vessel constriction caused by substances released by ischemia is not a likely complication of large-vessel CA occlusion.

MARKED DECREASE IN BLOOD FLOW AND INCREASE IN VASCULAR RESISTANCE DURING AND FOLLOWING COMPLEMENT ACTIVATED PLASMA INFUSION

Lyle J. Swenson, M.D., George A. Pantely, M.D., J. David Bristow, M.D., University of New Mexico, Albuquerque, New Mexico and Oregon Health Sciences University, Portland, Oregon

To investigate the acute effects of complement activation on blood flow, we infused zymosan activated plasma (ZAP) into the femoral artery of the isolated hind limb of 22 swine. Femoral artery blood flow (Q) decreased abruptly, was lowest at 1 minute of the infusion, then gradually returned towards control despite continued infusion. There was no significant change in femoral artery pressure (P) or femoral vein pressure, although systemic effects, as indicated by slightly lower aortic pressure, were observed at 1 minute. These changes were not prevented by alpha blockade (n=2) or selective granulocytopenia produced by cyclophosphamide (n=7), but were slightly attenuated by prior aspirin administration (n=3). No changes occurred during control infusion of heat decomplemented zymosan activated plasma (hd-ZAP).

	Control	1 min	5 min	10 min
P mm Hg	106±6	92±10	111±5	107±6
Q m/min	82±22	17±6*	29±9*	42±10*

Mean±SE *p<.01 ZAP vs. hd-ZAP

Following ZAP infusion, increased vascular resistance persisted as measured by slope of the PQ relationship during adenosine induced maximal vasodilation (5.9±1.3 ml/min/mmHg vs. 7.6±1.2 ml/min/mmHg control, p<.05). This effect was not altered by alpha-adrenergic blockade, granulocytopenia, or prior aspirin administration. Complement activated plasma infusion has marked acute effects on vascular resistance and blood flow. These effects appear to be mediated by activated complement components at the microvascular level.

DELAYED RECOVERY OF REGIONAL DIASTOLIC FUNCTION FOLLOWING REVERSIBLE ISCHEMIA IN CONSCIOUS DOGS. Martin L. Charlat, M.D., Padraig G. O'Neill, M.D., Craig J. Hartley, Ph.D., Robert Roberts, M.D., FACC, Roberto Bolli, M.D., Baylor College of Medicine, Houston, Tx.

Although recovery of systolic function following reversible myocardial ischemia is known to be delayed ("stunned" myocardium), the pattern of recovery of diastolic function is unknown. Thus, 8 conscious, unsedated dogs instrumented with epicardial Doppler probes to measure myocardial thickening underwent a 15-min occlusion of the anterior descending coronary artery followed by 7 days of reperfusion. No dog exhibited infarction (histology). Regional diastolic function was measured by: 1) mean rate to half end-diastolic thinning (RHEDT) and 2) late diastolic thinning fraction (TF). These two parameters reflect LV relaxation at 1/2 and 2/3 of diastole, respectively. Regional systolic function was measured by systolic thickening fraction (STF). Following reperfusion, the percent changes from preocclusion baseline were as follows: (mean±SE) (+p<0.05, *p<0.01 vs baseline)

	2h	4h	1 day	2 day	7 days
RHEDT	-48±9*	-45±6*	-18±8	+1.1±12.7	-5.7±7.0
TF	-36±9*	-26±8+	- 6±4	-3.6± 2.5	-3.4±1.7
STF	-54±8*	-45±9*	-17±4*	-0.6± 3.1	+2.9±7.2

Both RHEDT and TF were markedly decreased for at least 4 hours following reperfusion. At 1 day, neither RHEDT nor TF was significantly different from baseline, whereas systolic function (STF) was still depressed (p<.01). We conclude that after a brief, reversible ischemic episode, regional diastolic function remains severely impaired for several hours, although it recovers sooner than systolic function. These persistent abnormalities of relaxation of postischemic myocardium may be a major factor contributing to increased LV filling pressures in patients with transient myocardial ischemia.

Monday, March 10, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 3:00PM–4:00PM
Hall D, Georgia World Congress Center
Coronary Artery Disease—Basic

THE EFFECT OF PROSTAGLANDINS PGE1 AND PGE2 ON CHOLESTEROL EFFLUX FROM HUMAN MONOCYTE-DERIVED MACROPHAGES. Randee C. Goldstein, MS, Alan C. Wilson, PhD, and Peter T. Kuo, MD, FACC, UMDNJ-Rutgers Medical School, New Brunswick, NJ.

Cholesterol accumulation by monocyte-derived macrophages (MDM) in the arterial intima is the hallmark of early atherosclerosis. Recent work indicates increased cellular metabolism of lipoprotein cholesterol in the presence of interferon. Other workers report that prostaglandin PGE2 synthesis is also stimulated in interferon-treated MDM. This study was aimed at assessing the effect of PGE1 and PGE2 on MDM cholesterol metabolism. Human MDM were loaded with ^{3}H-labelled cholesteryl linoleate (^{3}H-CL) for 24h with cationized low density lipoprotein containing ^{3}H-CL (2000 cpm/nmol) as the sole core component. After 24h the mass content of CL was 78 nmol/mg cell protein. The lipid-laden cells were then incubated for 24 h in medium with high density lipoprotein to promote cholesterol efflux, alone as control, or with PGE1 or PGE2. Cholesterol efflux, measured by the amount of ^{3}H-CL recovered in the medium, increased by 42% and 60% over control in the presence of PGE1 and PGE2 respectively. Cholesterol ester hydrolysis was increased two-fold measured by the decrease in ^{3}H-CL and increase in ^{3}H-free cholesterol, and cholesterol esterification by acylCoA-cholesterol:-acyltransferase was increased three-fold by both PGE1 and PGE2. Total cell ^{3}H-cholesterol content was decreased 10% in control cells, and fell by 16% and 36% when incubated with PGE1 and PGE2 respectively. We conclude that prostaglandins PGE1 and PGE2 actively modulate cholesterol metabolism in MDM, increasing both turnover and efflux of cholesterol.

COD LIVER OIL SUPPLEMENTATION INHIBITS CORONARY ATHEROSCLEROSIS IN SWINE - Bonnie H. Weiner, MD, FACC, IS Ockene,MD,FACC, PH Levine,MD, M Fisher,MD, H Cuenoud,MD, AS Daoud,MD, J Jarmolych,MD, BF Johnson,MD, M Johnson,BS, J Hoogasian, MA. UMass Medical School, Worcester, MA

To determine whether cod liver oil (CLO) supplementation in a swine model of coronary atherosclerosis inhibits atherogenesis, 6 animals received 30 ml of CLO/day in addition to a high cholesterol, high fat (HCHF) diet and were compared to 11 animals who received the HCHF diet alone. All animals underwent balloon abrasion of the LAD after 3 wks on their respective diets. Plasma lipid, platelet fatty acid, serum thromboxane B_2,and 6-keto-$PGF_{1\alpha}$ values were determined at baseline, 3 wks, 4mos and 8 mos. At 8 mos all animals were sacrificed by perfusion fixation and the coronary arteries subjected to morphometric analysis. CLO had no effect on plasma lipid levels. Platelet arachidonate fell from 24.5±2.5 to 11.8±1.1% (p<.02) in the CLO group and was unchanged in the controls. Platelet eicosapentaenoic acid was only detected in the CLO group and was 8.0±.8% at 8 mos. Thromboxane B_2 fell from 14974.4±12295 to 534.3±358.4 and 6-keto-$PGF_{1\alpha}$ from 270.1± 192.6 to 51.2±15.9 pg/0.1 ml (p<.05 for both) in the CLO group; they were unchanged from baseline in the controls. Morphometric analysis of 407 segments from the control group and 172 from the CLO group demonstrated:

	%diseased	% ≥20% stenosis	%segments with CA^{++}
control	87.5	60.4	43.7
CLO	68.0	7.6	3.4
	p<.001	p<.001	p<.001

CLO supplementation inhibits the development of coronary atherosclerosis in this model. This may be mediated by changes in platelet fatty acids and prostaglandins, but not by plasma lipids. The data are consistent with the observed reduction in cardiovascular mortality in populations with a diet rich in marine oils.

STIMULATION OF CHOLESTERYL ESTER SYNTHESIS IN MACROPHAGES BY VLDL FROM THE WHHL RABBIT, A MODEL FOR FAMILIAL HYPERCHOLESTEROLEMIA Toru Kita, M.D., Masayuki Yokode, M.D. and Chuichi Kawai M.D., Kyoto University, Kyoto, Japan.

We have previously demonstrated that atherosclerotic plaques of WHHL rabbit are filled with foam cells. To study the mechanism of the formation of foam cells in vitro, we incubated macrophage with lipoproteins from WHHL rabbit. This WHHL rabbit, an animal model of human familial hypercholesterolemia, has severe hypercholesterolemia, cutaneous xanthomas and fulminant atherosclerosis including coronary atherosclerosis because of the deficiency of LDL receptor. When incubated with mouse peritoneal macrophages, the VLDL from WHHL rabbit (WHHL-VLDL) stimulated cholesteryl [^{14}C]oleate synthesis 124-fold more than did VLDL from the normal Japanese White rabbit (control-VLDL). The enhancement in cholesteryl ester synthesis and accumulation of WHHL-VLDL was due to the presence of a high affinity binding receptor site on the macrophage cell surface that mediated the uptake and lysosomal degradation of WHHL-VLDL. Competition studies indicated that the receptor for WHHL-VLDL was different from that previously described for low density lipoprotein (LDL) or human acetylated low density lipoprotein (acetyl-LDL), but that there was cross competition with β-VLDL. These results suggest that macrophages possess a high affinity receptor that recognizes the cholesterol-rich VLDL present in the plasma of the WHHL rabbit and that the receptor which mediates ingestion of WHHL-VLDL leads to cholesteryl ester deposition within macrophages. Thus the uptake of the cholesterol-rich VLDL from the WHHL rabbit by macrophages in vivo may play a significant role in the pathogenesis of atherosclerosis in the WHHL rabbit.

SUPPRESSION OF ATHEROGENESIS IN CHOLESTEROL-FED RABBIT WITH A LOW-DOSED CALCIUM ANTAGONIST (PN 200 110)

Jubran B. Habib, M.D., Claus Bossaller, M.D., Philip D. Henry, M.D.

Previous studies on anti-atherogenic effects of calcium antagonists have yielded in part conflicting results. In these experiments, drug doses administered were 10 to 100 times higher than those used clinically, and the possibility that the effects were related to reductions in arterial pressure was not excluded. To determine whether the anti-atherogenic action of calcium antagonists is related to arterial hypotension, we have fed rabbits a 1% cholesterol diet and randomly assigned them to placebo (P;n=14 rabbits) or drug treatment with the new calcium antagonist PN 200 110 (PN; n=14). The drug was given orally, 0.3mg/kg/day, which corresponds to a low dose in man. Diurnal arterial pressure profiles in the conscious state at 2-week intervals revealed no significant differences (P>.1) between P and PN. After 10 weeks before killing the rabbits, plasma cholesterol, phospholipids and triglycerides did not differ between groups, mean values (in mg/dl) averaging 2140±116, 792±49 and 122±15 for P, and 2012±115, 683±43 and 103±16 for PN. In P rabbits aortic lesions stainable with Sudan IV covered 52±5% of the intimal surface area and the aortic cholesterol concentration was 72±6 mg/g protein. Corresponding values for aortas from PN were significantly lower and averaged 36±5% (p<.03) and 52±3 mg/g protein (p<.03). Thus, low-dosed PN 200 110 exerted no hypolipidemic or hypotensive effects. Despite marked elevations in plasma cholesterol the drug suppressed structural and biochemical changes of atherosclerosis.

VASCULAR RESPONSIVENESS IN PORCINE CORONARY ARTERIES IS ALTERED BY AN ATHEROGENIC DIET

Rose Marie Robertson, M.D., F.A.C.C., Maria Victoria Tantengco, M.D. Charles R. Prince, M.D., Thomas B. Gore, M.D., James B. Atkinson, Renu Virmani, M.D., Jack N. Wells, Ph.D., Vanderbilt University., Nashville, TN.

To evaluate the effect of hypercholesterolemia on vascular responsiveness, we characterized the concentration-response (CR) relationship to adrenergic and cell-derived agonists in epicardial coronary arteries from Pittman-Moore minature swine on control and atherogenic diets.Coronary arterial rings 2-3 mm wide were equilibrated at 1 gm tension in Krebs-Ringer-bicarbonate at 37° C, gassed with 95% O_2-5% CO_2 at pH 7.4. No atherosclerosis was seen histologically. Cumulative CR curves (10^{-9}-10^{-4} M) were performed and results expressed as percent of the maximum response to KCl.

Agonist	Mean ED_{50} (μM) ± SEM Control (n=5)	Hypercholesterol (n=9)	P value
Epinephrine(EPI)	3.4 ± 1.6	2.7 ± 0.8	0.341
Isoproterenol(ISO)	0.1 ± 0.02	3.3 ± 1.1	0.039
Histamine(HIST)	9.4 ± 1.0	7.2 ± 0.9	0.003
Serotonin(5HT)	1.0 ± 0.3	1.0 ± 0.3	0.979

Although there was no significant difference in ED50 for EPI or 5HT, maximum contraction was significantly increased for both EPI (p=0.003) and 5HT (p=0.002). There was no dose response relationship between cholesterol level and reactivity for EPI, HIS, or SER, in that rings from animals with more severe hypercholesterolemia (234-474 mg%) were similar to those from control animals; the greatest difference was seen in animals with moderate hypercholesterolemia (131-215 mg%). Thus, although hypercholesterolemia shifts coronary reactivity towards a more easily vasoconstricted state, other factors than plasma cholesterol per se appear to be operative.

VERAPAMIL AND DIET HALT PROGRESSION OF ATHEROSCLEROSIS IN CHOLESTEROL FED RABBITS

R. Sievers, B.S., T. Rashid, M.D., J. Garrett, M.D., S. Blumlein, M.D., F.A.C.C., W. Parmley, M.D., F.A.C.C., University of California, San Francisco, Ca.

We previously showed that verapamil (V) suppresses aortic atherosclerosis (ATH) in cholesterol (C) fed rabbits. To evaluate the effects of oral V and normal (N) diet on regression, we studied groups of 5-8 rabbits each for 24 weeks (WK). All groups had a C diet for the first 12 WK. Group I was then sacrificed and had 38% aortic plaque:

GROUP	DIET (WK 1-12/ 13-24)	DRUG (Wk 1-12/ 13-24)	%AORTIC Plaque	VERAPAMIL Level(ng/ml)
I	C/	-/	38 ± 24(SD)	-
II	C/C	-/-	80 ± 8	-
III	C/N	-/-	78 ± 22	-
IV	C/C	V/V	54 ± 10	54 ± 59
V	C/C	-/V	70 ± 23	32 ± 24
VI	C/N	-/V	46 ± 24	41 ± 35

During WK 13-24, Group II (C diet) and Group III (N diet) had similar aortic plaque (80 and 78%). Group IV was treated with V for 24 WK and had less ATH (54%) than Group II (80%). In Group V, treatment with V during WK 13-24 did not significantly reduce Ath (70%) compared to Group II (80%). In Group VI, N diet and V during WK 13-24 significantly reduced ATH (46%),compared to Group II (80%), and Group III (78%), (p<.05). We conclude that combined V and N diet can halt the progression of ATH after a 12 WK C diet in rabbits.

DISADVANTAGES OF ARGON LASERS FOR ANGIOPLASTY.

Martin B. Leon, MD, FACC, David J. Underhill, MD, Paul D. Smith, PhD, William C. Roberts, MD, FACC, Richard E. Clark, MD, FACC, Stephen E. Epstein, MD, FACC and Robert F. Bonner, PhD, NHLBI, Bethesda, Md.

An evaluation of Argon laser (Ar) interactions with human cadaver coronary arteries (n=9, target sites = 124) provides evidence for serious limitations which may compromise the safety and efficacy of Ar angioplasty. Using continuous Ar through fibers (100-600um) with varying lasing parameters (.65-6w for 1-60s, fiber-target distance=0-4mm, media=air, saline, and blood) we found: (1) Explosive Tissue Ablation. Infrared surface thermography and histology indicate that initial crater formation is an inefficient, single large-step process resulting from explosive vaporization of tissue water after surface temperature exceeds 100°C with liberation of gaseous and particulate by-products. (2) Marked Thermal Diffusion. Intense crater charring was surrounded by a broad transmural histologic zone of injury (zoi); from quantitative ocular micrometry, zoi surface area averaged >8x crater surface area. Histologic thermal injury occurred at intimal and adventitial temperatures above 45°C and required only 4% of the energy necessary to initiate tissue ablation. (3) Variable Thermal and Ablative Effects. Lasing efficiency and thermal diffusion varied with power density, lasing media, plaque composition and especially fiber-target distance. Best Ar ablative effects were achieved by advancing the fiber to maintain tissue contact thereby reducing thermal diffusion; however, the direction, magnitude, and rate of atheroma ablation were difficult to control predisposing to vessel wall perforation. Hence, Ar angioplasty is nonselective for plaque, imprecise, associated with severe thermal injury, and results in variable ablative effects which may restrict future clinical applications.

PERSISTENCE OF ANAEROBIC GLUCOSE UTILIZATION IN REPERFUSED MYOCARDIUM.
M. Schwaiger, R. Neese, W. Wijns, J. Wisneski, M. Grover-McKay, M.E. Phelps, H.R. Schelbert, and E. Gertz, UCLA School of Medicine, Los Angeles, and UCSF School of Medicine, San Francisco, California.

Positron emission tomography (PET) demonstrates increased F-18 deoxyglucose (FDG) uptake in reperfused myocardium consistent with enhanced glucose utilization. To determine the metabolic fate of glucose (gluc), [6-^{14}C] labeled glucose and [^{13}C] lactate were infused in 4 of 7 dogs in which PET demonstrated increased FDG uptake in the segment that was reperfused for 24 hrs after a 3 hr balloon occlusion of the left anterior descending (LAD). Blood samples were withdrawn simultaneously from left atrium, LAD vein and coronary sinus (CS) for determining chemical and labeled glucose, CO_2 and lactate concentrations. Compared to the entire heart (CS sample) extraction of glucose in the reperfused myocardium (LAD vein) was 63% higher and averaged 0.35 ± 0.15 μmol/ml. 81 ± 5% of glucose entered glycolysis, of which 36 ± 11% was oxidized and 64 ± 11% released as lactate. The fraction of glucose oxidized was inversely related to plasma free fatty acid levels (r=-0.86). Thus, increased FDG uptake in reperfused myocardium reflects increased glucose utilization in surviving tissue. Oxidation of glucose likely occurs in cells which still respond to normal regulatory mechanisms (i.e., FFA levels), as compared to injured cells which metabolize glucose largely anaerobically. Therefore, the increased FDG uptake seen on PET reflects primarily anaerobic glycolysis which persists for prolonged time periods after reperfusion.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #313/314
Critical Evaluation of Doppler Echocardiography

COLOR FLOW MAPPING DOPPLER UNDERESTIMATES JET WIDTH WHEN COMPARED TO LASER DOPPLER ANEMOMETRY IN AN IN VITRO MODEL OF ADULT AORTIC STENOSIS.
David J. Sahn,M.D., F.A.C.C., Tadashi Tamura, C.Ph., M.S., Lilliam Valdes-Cruz, M.D., F.A.C.C. Ren Woo, Hsing-Wen Sung, Ajit Yoganathan,Ph.D., Univ of Calif, San Diego, CA.
In this study we evaluated color flow mapping Doppler (CD) in an in vitro model of aortic stenosis with interrogation from the "arch" (transducer to valve distance 8 cm). We measured jet width at peak systole by CD mapping, 25mm from the valve ring where measurements by laser Doppler anemometry(LDA) were made. For 20 individual gradients (GRAD) (15-105 mmHg) through stenotic (0.5-2.8cm^2) bioprosthetic valves, results showed consistent underestimation by CD compared to LDA jet width (r=0.42) with the greatest degree of underestimation in mild stenoses with low velocities. When CD was compared to LDA jet widths for moderate and severe stenosis only (GRAD >45mmHg)(N=13), a correlation of r=0.90 was obtained but still with slight underestimation of jet width by CD. For the 20 GRAD, jet width by LDA was narrower in the more stenotic valves. As an alternate approach, the length of formation of the acceleration jet proximal to the stenotic valves at peak ejection was imaged by CD and correlated well to actual gradients (r=0.88) suggesting that in more severe stenosis, acceleration begins at a longer distance proximal to the valve. Our results suggest that low velocity cutoffs and signal-to-noise problems in the CD method at interrogation distances similar to those required in adult aortic stenosis from suprasternal or high right parasternal views may substantially limit the accuracy of direct noninvasive jet width measurement. Alternative methods such as measuring the distance at which acceleration begins in the outflow tract proximal to the valve, assessed from apical views may prove important in adult aortic stenosis.

COMPUTER ANALYSIS OF COLOR DOPPLER IMAGES FOR QUANTITATIVE ASSESSMENT OF FLOW JETS IN A PHANTOM MODEL
Ann Bolger, MD, Neal Eigler, MD, J Martin Pfaff, BS, Gerald Maurer, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA

Visual inspection of Doppler Color Flow Mapping (CFM) images allows only subjective assesment of cardiac flow patterns. To determine if automatic digital processing of CFM data could quantify volume (V) and kinetic energy (KE) transfer in flow jets, we interfaced a CFM machine with a image processing computer and acquired on-line images at 10 frames/sec. Forty-six power injections of a cornstarch solution (volumes 2-20 ml, flow rates 2-20 ml/s) were performed via 3 different orifice areas (OA) into a submerged phantom chamber. Each pixel represents a volume due to ultrasonic beam thickness; therefore jet V of each frame was calculated as the sum of pixels displaying velocity. Jet V was integrated over the duration of injection and compared to known injection V. Jet KE was estimated by quantitative CFM as the sum of (number of pixels x colorimetric pixel velocity^2) and was compared to the predicted KE [1/2 x injectate mass x (flow rate/OA)^2]. CFM integrated jet V was reproducible for paired injections (r=0.99), correlated with injection V (r=0.96, SEE=1.8 ml), but was specific for OA. Jet KE estimated by CFM was also reproducible (r=0.99), and correlated with predicted KE (r=0.96, SEE=2.1x10^3 ergs) up to 20x10^3 ergs and then plateaued due to aliasing. CFM measurement of KE was independent of OA. Conclusion: Quantitative computer analysis of CFM appears capable of accurate and reproducible calculation of jet kinetic energy as well as estimation of injection volume for a given orifice. This technique may ultimately allow for quantification of CFM jets in the setting of valvular regurgitation and intracardiac shunts.

IN VITRO STUDIES OF THE ACCURACY OF VELOCITY DETERMINATION AND SPATIAL RESOLUTION OF A COLOR FLOW MAPPING DOPPLER SYSTEM.
Tadashi Tamura, C.Ph, M.S., Lilliam M. Valdes-Cruz, M.D., F.A.C.C., David J. Sahn, M.D., F.A.C.C., Univ of Calif, San Diego, CA.
We tested a commercially available color flow mapping Doppler system (CD) [Irex Aloka 880, 3.5 MHz transducer (TX)] to image the steady flow of a suspension of cornstarch (1%) in water, flowing at known velocities through a series of tygon tubings (internal diameter (ID)=1.6 to 4.8 mm) and latex rubber tubings (ID = 7.9 to 15.9 mm) in a water tank. Flow through the tubes was imaged at 2-12cm and 18cm distances from the TX using the near and the far focus settings of the instrument. First, the color flow diameters were compared to the known ID of the tubings oriented at a 30°- 60° flow angle to the direction of interrogation to test lateral resolution. At <6 cm from the TX, the CD diameter obtained with the near and far focus settings correlated equally well with the actual ID (r=0.99, SEE =0.23mm; and r=0.99, SEE=0.17mm, respectively). Axial resolution was likewise excellent in this depth range, but results were gain dependent. At >6cm distance, CD measurements with the near focus overestimated the ID (up to 7 times the ID); the far focus also overestimated the ID but to a lesser degree (up to 1.8 times the ID of the 2.4mm tube). The lowest flow velocity color encoded by the instrument at 0° angle to flow was 3 cm/sec (133Hz) either towards or away from the TX. At a flow velocity of 50cm/sec, 6 cm distance from the TX and mid gain settings, flow through the 1.6mm tube barely color coded while flow through 2.4mm, 3.2mm and 4.8mm tubes was easily imaged. These results have direct implications in clinical studies for imaging small septal defects or when measuring CD flow diameters of vessels or valves for volume flow calculations.

A COMPARISON OF DOPPLER-ECHOCARDIOGRAPHIC METHODS FOR CALCULATING TRANS-MITRAL BLOOD FLOW IN A CANINE MODEL

Kathryn J Ascah, MD, William J Stewart, MD, Marco O Triulzi, MD, Linda D Gillam, MD, FACC, Arthur E Weyman, MD, FACC, Massachusetts General Hospital, Boston, MA

Accurate measurement of the valvular cross-sectional area is an important factor in the Doppler-2D-echocardiographic calculation of intracardiac blood flow. To compensate for the variation in mitral valvular cross-sectional area during diastole, several different methods for calculating the diastolic mitral valve area (MVA) have been described. To evaluate the relative accuracy of these methods for obtaining the effective MVA used in deriving Doppler mitral blood flow, we compared mitral blood flow calculated using 7 methods of measuring MVA, with known trans-mitral flow in a canine model. Mitral flow ranged from .44 - 4.6 l/min. MVA was computed from the maximal and mid-diastolic antero-posterior (AP) and 4-chamber (4C) annular dimensions assuming circular and elliptical configurations. Mitral blood flow was also calculated using the mean-to-max ratio method described by Fisher.

RESULTS:

METHOD		n	SLOPE	INTERCEPT	r	SEE
4Cmaximal	circle	33	1.18	.64	.84	.69
4Cmid	circle	34	1.4	.13	.78	.95
APmaximal	circle	50	.86	.37	.81	.57
APmid	circle	50	.93	.13	.81	.61
Ellipse	maximal	30	1.06	.33	.84	.62
Ellipse	mid	30	1.15	.16	.83	.69
FISHER		55	.89	.24	.88	.46

CONCLUSION: All methods yielded satisfactory results. Methods employing the AP dimensions underestimated flow, whereas those using the 4C overestimated flow. The elliptical methods result in slopes most closely approximating unity.

DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR SYSTOLIC PERFORMANCE - COMPARISON WITH DP/DT AND MINUTE WORK UNDER VARYING CONDITIONS.

Kenneth Wallmeyer, M.D., Terrence Cogswell, M.D., L. Samuel Wann, M.D., F.A.C.C., Kiran Sagar, M.D., F.A.C.C., Andrea Purnell, B.S., Donna Peterson, B.S., H. Sidney Klopfenstein, M.D., Ph.D., Medical College of Wisconsin, Milwaukee, Wi.

To investigate the ability of Doppler echocardiography of ascending aortic blood flow to assess left ventricular performance, seven open-chest dogs were studied under varying conditions of preload, afterload, and inotropy. Different loading conditions were achieved using occluders around the venae cavae and the descending aorta; changes in inotropic state were induced by dobutamine infusion (5 mcg/kg/min I.V.) and propranolol administration (1-2 mg/kg I.V.). LV anterior wall segment length (sonomicrometer crystals) was used as an index of preload, and mean aortic blood pressure (catheter tip transducer) as an index of afterload. Phasic ascending aortic blood flow (electromagnetic flow probe) and LV pressure (high fidelity transducer) allowed measurement of maximum aortic flow (Q_{max}), peak acceleration of flow (dQ/dt), minute work, and dp/dt. A continuous wave Doppler transducer applied to the aortic arch was used to measure peak aortic blood flow velocity and mean acceleration. Data from all hemodynamic states were pooled and analyzed by the least squares method of linear regression. Peak velocity correlated closely with minute work index ($r = .78$; $p<.001$) and Q_{max} ($r = 0.71$; $p<.001$) and less well with dP/dt ($r = 0.63$; $p<.001$). Mean acceleration of aortic blood velocity was most closely correlated with peak dP/dt and dQ/dt ($r = 0.83$ and 0.70, respectively, $p<.001$), and less well with minute work ($r = .49$, $p<.005$). In conclusion, Doppler measurements of peak aortic blood flow velocity and mean acceleration offer an effective means to assess acute changes in LV performance under conditions of widely varying preload, afterload, and contractility.

ASSESSMENT OF LEFT VENTRICULAR-SYSTEMIC ARTERIAL COUPLING: A NEW APPLICATION OF DOPPLER ECHOCARDIOGRAPHY

Alex Neumann, Kenneth M. Borow, MD, Sajeev G. Shroff, PhD, Dina Janzen, Dianne Altman, Univ of Chicago, Chicago, IL

Doppler echocardiography has allowed noninvasive assessment of LV and AO flow in humans. Recently, calibrated carotid pulse tracings (CPT) have been shown to accurately measure instantaneous LV ejection pressure and wave morphology. The combination of simultaneously recorded AO flow (from suprasternal Doppler) and pressure (from CPT corrected for pulse transmission time) allows assessment of instantaneous LV and systemic arterial hemodynamics. This is particularly important since traditional indices (such as SVR) use mean pressure (Pm) and flow and thus describe the heart as a non-pulsatile pump. This type of assessment may lead to underestimation of LV energetics. Total LV power (TP) incorporates instantaneous AO pressure and flow and therefore can be used as an index of performance of the coupled LV-arterial system. TP is more sensitive to changes in hemodynamic conditions than either pressure or flow considered alone. TP can be divided into: (1) steady power (SP) which maintains forward blood flow and (2) oscillatory power (OP) which is lost in pulsations of the arterial system. Only SP results in effective flow. The efficiency of the LV-arterial coupling can be assessed as OP/TP.

Using the integral of AO pressure and flow, Pm, cardiac output (CO; L/min), SVR (dyne-sec-cm^{-5}), TP, SP, and OP (mW) were calculated in 16 normal subjects (age: 38±15 years). AO root size was measured by 2D echo and blood flow calculated. Heart rate was 68 ± 10 bpm.

	Pm	CO	SVR	TP	SP	OP	OP/TP
Mean	96	6.1	1290	1580	1260	280	.17
SD	9	1.0	200	320	380	80	.03

These data establish normal values for LV power using this technique. If only SVR were determined, OP would be neglected. However, OP accounted for 17% of TP. Thus, a detailed noninvasive assessment of the LV-arterial coupling is now possible.

Tuesday, March 11, 1986
10:30AM-12:00NOON, Room #313/314
Doppler Echocardiography for Mitral Valve Disease

DOPPLER DIAGNOSIS OF MITRAL REGURGITATION: REFINING THE CRITERIA

Tze-Yu Dang, MD; John A. Mallery, MD; Julius M. Gardin, MD, FACC; Alice Allfie; Sandy Clark; Walter L. Henry, MD, FACC. University of California, Irvine, CA

Despite the sensitivity of pulsed Doppler echocardiography (echo) in detecting mitral regurgitation (MR), recent reports have suggested a high-incidence of false-positive studies for MR in normal subjects. To devise more specific criteria for MR, pulsed Doppler and left ventriculography were compared in 86 patients undergoing clinically indicated cardiac catheterization. In addition, 20 normals were studied by Doppler. Twenty-seven of 86 patients (31%) and 4 of 20 normals (20%) had systolic turbulence in the left atrium by Doppler echo. Ten of these 27 patients had MR by angiography: all 10 demonstrated holosystolic turbulence in the left atrium, mapped in both the apical four- and two-chamber views, with peak jet flow velocity (PFV) >150 cm/sec. Of the 17 of 27 patients with no MR by angiography, only 2 patients fulfilled all above Doppler criteria and were falsely identified as having MR. Among the 20 normals, 4 demonstrated systolic (3 had holosystolic) turbulence in the left atrium, but PFV in all was less than 150 cm/sec. Sensitivity and specificity of the combination of Doppler PFV >150 cm/sec plus holosystolic turbulence in both apical views for detecting MR (compared with angiography) were 83% and 100%, respectively. We conclude that systolic turbulence can be detected in the left atrium in many normals and patients without angiographic evidence of mitral regurgitation. However, holosystolic turbulence recorded in both apical views with peak flow velocity >150 cm/sec identifies patients with mitral regurgitation by angiography.

EXERCISE DOPPLER ECHOCARDIOGRAPHY IN PATIENTS WITH ISOLATED MITRAL STENOSIS: CLINICAL FEASIBILITY.

Eugenio Moro, M.D., Folkert J. ten Cate, M.D. and Jos Roelandt, M.D., F.A.C.C., Thoraxcenter - Erasmus University Rotterdam, The Netherlands.

Exercise (Ex) raises heart rate (HR) and cardiac output (CO) and is helpful in the determination of dynamic mitral gradient (MG) in patients (pts) with mitral stenosis (MS) but has important practical limitations during cardiac catheterization (cath). The feasibility of combined two dimensional (2D) and continuous wave Doppler (CWD) echocardiography (E) during Ex was tested in 7 pts (mean age 33 years, 5 male and 2 female) with pure MS and sinus rhythm. Baseline 2D and CWD-E were performed, CWD was repeated after 1 minute of supine bicycle Ex at workloads of 25 and 50 Watts (W). Mitral valve area (MVA) as determined in short axis parasternal view, was considered fixed. From the velocity tracings these parameters were derived: mean flow velocity (MFV), mean MG, diastolic filling period (DFP). Stroke volume (SV) was calculated as DPFxMVAxMFV and CO is the product of SVxHR. Results are given as mean ±/standard deviation: *p < 0.05.

	Baseline	25 W	50 W
MVF m/sec	1.4 ± 0.1	1.9 ± 0.2*	1.9 ± 0.2*
DFP m/sec	508 ± 70	340 ± 45*	355 ± 48*
MG mmHg	9 ± 3	16 ± 8*	16 ± 9*
MVA cm^2	1.4 ± 0.4		
HR b/min	65 ± 6	89 ± 9*	90 ± 7*
SV m/min	82 ± 4	76 ± 8	79 ± 7
CO l/min	5.3 ± 0.6	6.5 ± 0.5*	6.7 ± 0.5*

Doppler is a non-invasive and reproducible tool which provides relevant information about the dynamic responses to Ex in pts with MS which occur early during Ex and can substitute for cath in most patients.

DOPPLER MITRAL PRESSURE HALF-TIME IS NOT AN INDEPENDENT PREDICTOR OF MITRAL VALVE AREA.

Kiran B. Sagar, M.D., F.A.C.C., and L. Samuel Wann, M.D., F.A.C.C., Medical College of Wisconsin and Zablocki VA Medical Center, Milwaukee, Wi.

Mitral valve area can be estimated from the mitral Doppler velocity flow profile using the pressure half-time and an empiric constant. This constant does not take into account differences in cycle length or transvalvar gradient and flow. To determine the influence of these variables on the pressure half-time method, we performed pulsed Doppler echoes at rest and during symptom-limited supine bicycle exercise in 10 patients with mitral stenosis. The mean gradient across the mitral valve was determined from the flow velocity integral and the mitral valve area calculated as MVA = $\frac{220}{\text{pressure half-time}}$.

	Rest	Exercise
Heart Rate	74.5±14.4 bpm	110.1± 7.5 bpm*
Mean Mitral Gradient	9.4± 4.6 mm Hg	18.3± 7.2 mm Hg*
Pressure Half-Time	225.2±62.0 msec	184.0±49.0 msec**
Mitral Valve Area	1.0± 0.3 cm^2	1.2± 0.3 cm^2**

(mean±SD)

* P<.001 Rest vs Exercise

** P<.005 Rest vs Exercise

We conclude: 1) mitral valve area by the pressure half-time method varies with changes in heart rate, transvalvar gradient and flow, 2) since anatomic valve area does not change, the pressure half-time method probably underestimates true valve area at higher heart rates and flows, 3) caution is advised in using the pressure half-time method to estimate valve area in patients with rapid heart rates and increased transvalvar flow.

EFFECT OF AORTIC REGURGITATION ON THE DOPPLER-DERIVED MITRAL PRESSURE HALF-TIME.

Kwan-Leung Chan, M.D. and A. Jamil Tajik, M.D., F.A.C.C., Mayo Clinic, Rochester, MN.

Mitral stenosis can be difficult to diagnose in the presence of aortic regurgitation. Doppler-derived mitral pressure half-time (MHT) has been useful in quantitating the severity of mitral stenosis and estimating the mitral orifice area. MHT has been reported to be independent of mitral regurgitation and heart rate. To determine the effect of significant aortic regurgitation on MHT, 17 patients (12 males, 5 females; mean age, 47 yr; range, 15-79) with nonstenotic mitral valve were prospectively evaluated by continuous-wave (CW), pulsed-wave (PW), and color flow Doppler studies. Significant aortic regurgitation, defined by the regurgitant stream tracking to or beyond the papillary muscle on color flow imaging, was present in each case. The regurgitant jet was directed to the anterior mitral leaflet in 14 patients and toward the ventricular septum in 3 patients. In 9 of the 14, but none of the 3, CW Doppler signal was inadequate for calculation of MHT because of contamination by the aortic regurgitation signal. PW study yielded good mitral inflow signal in each case. The mean MHT by PW was 66 ms (range, 43-100). In the 8 patients who had both CW and PW measurements, MHT was similar by both techniques (68 ms vs 67 ms) but the early diastolic flow velocity was higher with CW (1.10 m/s) than with PW (0.72 m/s) ($P < 0.05$). Thus, Doppler-derived MHT does not appear to be affected by significant aortic regurgitation. Both CW and PW can be used to derive MHT, but PW is preferable when the aortic regurgitant jet is directed toward the anterior mitral leaflet because signal contamination by aortic regurgitation can be avoided.

QUANTIFICATION OF MITRAL STENOSIS: A COMPARATIVE STUDY OF TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY AND INTRACARDIAC HEMODYNAMICS.

Melvin A. Gonzalez, M.D., John S. Child, M.D., F.A.C.C., and Janine Krivokapich, M.D., F.A.C.C. UCLA School of Medicine, Los Angeles, CA

Forty-three pts with mitral stenosis (MS) were studied using 2-D and Doppler echo to assess the relationships between cath-derived pressure gradient half-time (P½), Gorlin formula mitral valve area (MVA), and 2-D echo MVA as compared to MVAs determined from Doppler velocity half-times (t½s). A reliable line drawing method for measuring t½s in the presence of non-linear initial Doppler velocity profiles was determined to be a line using the mid-diastolic Doppler profile. The success rate of each method in quantitation of MS was assessed. MVA was quantifiable in 91% of pts using 2-D or Doppler, and in 99% if both techniques were used. MVAs from 2-D and Doppler ($MVA(cm^2)=220/t½$ (msec)) were compared to MVAs calculated from Gorlin formula and cath-derived P½s in 27 pts. Doppler t½s and hemodynamic P½s had an inverse exponential relationship to Gorlin formula MVAs (r=-0.81 and -0.89, respectively); 220 msec approximated a valve area of 1 cm^2. In the absence of mitral regurgitation both 2-D and Doppler accurately predicted Gorlin formula MVAs (r=0.73 and 0.95, respectively). Doppler and 2-D MVAs were strongly correlated (r=0.89). In the presence of mitral regurgitation, 2-D MVAs correlated weakly with Gorlin formula MVAs (r=0.38) but a strong relationship (r=0.90) persisted between Doppler and Gorlin formula MVAs.

Thus, 2-D echo provides an accurate anatomic orifice area whereas Doppler provides additional information regarding physiologic significance of any given MVA. The 2 techniques are accurate and complementary in quantification of MS. To achieve these results, it was important to establish an accurate and reproducible Doppler velocity line drawing method which does not use early non-linear portions of the curves.

CHARACTERIZATION OF MITRAL STENOSIS VELOCITY JET BY COMBINED COLOR FLOW IMAGING AND GUIDED CONTINUOUS-WAVE DOPPLER.

Bijoy K. Khandheria, M.D., A. Jamil Tajik, M.D., F.A.C.C., Guy S. Reeder, M.D., F.A.C.C., Mark J. Callahan, M.D., Rick A. Nishimura, M.D., F.A.C.C., Fletcher A. Miller, M.D., F.A.C.C. and James B. Seward, M.D., F.A.C.C., Mayo Clinic, Rochester, MN.

Color flow imaging (CFI), a new Doppler technology, permits real-time visualization of intracardiac blood flow. Mitral stenosis jet velocity profiles were defined in 42 patients (35 females, 7 males; mean age 58 yr, range 26-83 yr; mean body surface area 1.65 m^2, range 1.44-2.27 m^2). All had satisfactory CFI. Frequency aliasing resulting in color reversal--producing a central blue zone surrounded by shades of red/yellow (candle flame appearance)--was noted in all patients. Variable jet configurations were identified: central and directed apically in 18/42 (43%); central and directed laterally (scimitar shape) in 18/42 (43%); and unusual shape in 6 (14%) (mushroom-like in 2, bifid in 2, posterior in 1, and medial in 1). The jet configuration allowed visualization of maximum velocity vectors, permitting guided continuous-wave Doppler (CWD) examination. Diastolic half-times ranged from 90 to 280 msec. On the basis of composite analysis, stenosis was mild in 16, moderate in 20, and severe in 6. Associated mitral regurgitation was detected in 21/42 (50%) and tricuspid regurgitation, in 22/42 (52%). Conclusion: 1. A mitral stenosis jet was visualized and characterized in all patients--central in 86% and eccentric in 14%. 2. Visually guided CWD enabled confident evaluation and quantitation of Doppler severity of the stenotic valve. 3. CFI promises noninvasive visualization of jet direction and configuration and directs spectral Doppler assessment. CFI with guided CWD provides more comprehensive information about mitral stenosis.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #260/261
Outcomes Following Angioplasty

LATE ANGIOGRAPHIC OUTCOME FOLLOWING SUCCESSFUL MULTIPLE LESION PTCA

Michel Vandormael, M.D., Ubeydullah Deligonul, M.D., Ali Medhirad, M.D., Michael Harper, M.D., F.A.C.C., Bernard Chaitman, M.D.,F.A.C.C. St. Louis University School of Medicine, St. Louis, Missouri.

There are few late angiographic follow-up data in patients (pts) undergoing multilesion-multivessel (ML-MV) PTCA. Prior to December 1984, 171 consecutive pts underwent ML-MV PTCA at St. Louis University. PTCA was clinically successful (functional improvement and no in-hospital complications) in 158 pts (92%). Of 437 attempted lesions, 385 (88%) were successfully dilated (>30% reduction diameter and residual lesion <50%) with balloon inflation times and inflation pressures ranging from 30-90 sec and 6-10 atm. Aspirin, dipyridamole and nifedipine were continued for 6 mo. Among the 158 pts with a clinical success, 86(54%) underwent coronary angiography an average of 6.4+3.7 months (mo) after PTCA. The restenosis (R) rate (diameter increase $\geq$50%) of the 200 lesions dilated in the 86 pts was 34%.

Among the 47 pts studied because of recurrence of angina, 74% had R, an average of 5.7 (range 1-20) mo after the procedure. The R occurred at more than one dilation site in 40% (14/35) of the pts. Among the 12 symptomatic pts without R, 3 developed a new stenosis >50% in an area other than the dilation site; 9 had no disease progression; 18 pts underwent repeat PTCA and 7 pts had CABG. Among the 39 asymptomatic pts studied electively 7.4 (range 2-22) mo after PTCA, 11(28%) pts had R. The R occurred at more than one dilation site in 18% (2/11) of the pts. Three asymptomatic pts with R had a repeat PTCA and the remainder received medical therapy. Thus, the initial success of multilesion/multivessel PTCA is not compromised by an unacceptable restenosis rate/lesion in the year following the procedure. In pts with recurrent symptoms, the predominant cause is restenosis as opposed to disease progression. Restenosis frequently occurs (46%) at more than 1 dilation site.

RECURRENCE RATE AFTER PTCA IN RELATIONSHIP TO THE INITIAL LENGTH OF CORONARY ARTERY NARROWING

Rainer Uebis M.D., Rainer von Essen M.D., Jürgen vom Dahl M.D., Hermann J. Schmitz M.D., Katja Seiger, Sven Effert M.D.
Dept. of Internal Medicine I, RWTH, Aachen, West Germany.

In 100 consecutive patients (pts) with one-vessel disease undergoing elective percutaneous transluminal coronary angioplasty (PTCA), the intial length of the lesion (i.e. the section with at least 50 % narrowing of the intial vessel diameter) was calculated and compared to the recurrence rate. A control angiogram after 5.9 ± 2.1 months could be obtained in 89 cases. 3 definitions of recurrence were compared; ①: long term gain of diameter $\leq$20 %; ②: loss of initial gain $\geq$50 %; ③: ② or increase in diameter stenosis $\geq$30 % in comparison to narrowing immediately after PTCA. In addition, the frequency of a localized intimal lesion – not exceeding the length of the inflated balloon – in correlation to the recurrence rate was analysed.

Results:

GROUP	n	LENGTH OF STENOSIS / MM	RATE OF RECURRENCE DEF ③ %		n	DISS. ⊕	DISS. ⊖
A	22	< 2	4.5		1	0	1
B	24	2 – 2.9	33.3	*	6	2	4
C	24	3 – 3.9	33.3		7	4	3
D	19	≥ 4	31.6		5	0	5
Σ	89		25.9		19	6	13

*: p 0.05 ; DISS ⊕: recurrence def. ③ and localized intimal lesion
DISS ⊖: recurrence def. ③ without localized intimal lesion

The recurrence rate according to definition ③ (25.9 %) statistically was not different in comparison to def. ② (24.8 %) resp. def. ① (19.2 %).

Conclusions: In pts with very short stenoses (group A) the frequency of recurrence after successful PTCA is significantly lower as compared to group B. An additional increase of the initial length (groups C + D) does not result in a further increase of the recurrence rate. In addition, recurrence tends to be less frequent if PTCA caused a localized intimal lesion. However, the number of pts is limited and further confirmation of these data is needed.

THE RESULTS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) IN POST INFARCTION ANGINA PECTORIS.

Geoffrey W. Holt, M.B., B.S., Bernard J. Gersh, M.B., Ch.B., FACC, David R. Holmes, Jr., M.D., FACC, Ronald E. Vlietstra, M.B., B.S., FACC, Guy S. Reeder, M.D., FACC, John F. Bresnahan, M.D., FACC, Hugh C. Smith, M.D., FACC. Mayo Clinic, Rochester, MN.

Between May 1980 and Jan. 1985, 69 patients (pts) underwent PTCA for severe angina within 30 days (mean 12.6) of myocardial infarction (MI). All 69 pts met WHO criteria for MI. There were 32 pts with Q wave MIs (Grp I) and 37 pts with non Q wave MIs (Grp II); mean age was 57 years for both groups. PTCA was successful in 80% (55 pts). In Grp I, PTCA was successful in 69% (22 pts); of the 10 pts who failed PTCA, 5 had emergency coronary artery bypass (CAB) and 3 elective CAB. In Grp II, PTCA was successful in 89% (33 pts); of the 4 pts who failed, 3 had emergency CAB (1 death) and 1 elective CAB. 25% (17 pts) of the total group had angioplasty of an occluded artery which was successful in 7 of 12 Grp I pts (58%) and 5 of 5 Grp II pts (100%).

Tabulated are the late results of the pts successfully dilated (mean follow up 21 months).

	Death	Recurrent MI	Class III-IV Angina	CAB	Repeat PTCA
Grp I n=22 (%)	0	1(5)	1(5)	3(14)	2(9)
Grp II N=33 (%)	0	1(3)	0	2(6)	5(15)

In conclusion: (a) Early PTCA for severe angina post MI was effective and safe with an 80% overall success rate and a 2% mortality. (b) Survival after successful PTCA was excellent with no deaths during follow up. However, in this same group, there were 2 recurrent MIs and 13 pts (24%) had either severe angina or required repeat revascularization (CAB/PTCA).

INCIDENCE OF EARLY RESTENOSIS AFTER SUCCESSFUL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

Stephen Powelson, M.D., Gary Roubin, M.B., Ph.D, Hall Whitworth, M.D., Andreas Gruentzig, M.D., F.A.C.C. Emory University School of Medicine, Atlanta, Georgia

To define the incidence of restenosis early after PTCA, we prospectively performed arteriography 2 days after PTCA on 50 patients with successful dilatation of 70 lesions. Diameter stenoses (DS), measured with electronic calipers, were (mean±SD): DS pre PTCA: 68±16%, DS post: 29±13%, and DS at restudy: 33±14%. Presence or absence of intimal disruption (intraluminal defect or extraluminal contrast extravasation) was noted. Early recurrent stenosis (ERS) was defined as loss of 50% of initial DS gain, vs continued success (CS).

Early restenosis occurred in 7 of 70 lesions (10%). For lesions with ERS compared to lesions with CS, DS pre and DS post PTCA were similar but DS at restudy was higher: ERS vs CS, DS pre: 67±23% vs 69±17% (p=NS), DS post: 21±12% vs 30±12% (p=NS), DS at restudy: 50±16% vs 31±12 ($p<0.05$). Immediately after dilatation, 25 lesions (36%) had intimal disruption. The incidence of such disruption in lesions with ERS was 5/7 (71%) and in lesions with CS was 20/63 (32%) ($p<0.1$).

We conclude that early restenosis occurs in 10% of lesions after PTCA before discharge. Intimal disruption occurs commonly after PTCA and is more frequent in lesions with early restenosis. Long-term follow-up will clarify whether such changes persist or improve.

ANGIOGRAPHIC PATTERNS OF RESTENOSIS AFTER CORONARY ANGIOPLASTY OF MULTIPLE VESSELS.

Germano DiSciascio, M.D., Michael J. Cowley, M.D., F.A.C.C., George W. Vetrovec, M.D., F.A.C.C., Timothy C. Wolfgang, M.D., Medical College of Virginia, Richmond, Virginia.

Restenosis (RES) after PTCA is not infrequent but the angiographic patterns of recurrence after PTCA of multiple vessels (MV) have not been characterized. In order to assess this, angiograms were reviewed in 38 patients (pts) who developed clinical recurrence (CR) after PTCA of MV. CR was defined as return of symptoms after successful PTCA and RES of one or more lesions (loss of >50% of initial angiographic improvement). PTCA was successful in 97 lesions in these 38 pts (2.6/pt); 2 lesions were dilated in 22 pts, 3 lesions in 12 pts, 4 lesions in 3 pts, 5 lesions in 1 pt. Mean lesion severity was 85.3 ± 10% pre-PTCA and 42 ± 13% post-PTCA. In these pts with CR, RES occurred in 58 of 97 lesions (60%). Twenty pts (53%) had RES of a single lesion (11 pts with 1 of 2 lesions, 8 pts with 1 of 3 lesions, 1 pt with 1 of 5 lesions); 18 pts (47%) had RES of multiple lesions (11 pts with 2 of 2 lesions, 3 pts with 2 of 3 lesions, 2 pts with 2 of 4, 1 pt with 3 of 3, 1 pt with 3 of 4 lesions). Only 12 of 38 pts (31%) had RES of all lesions. Mean % improvement with PTCA was 43.4 ± 14% for all lesions and was not significantly different for lesions with and without RES. However, mean % stenosis post-PTCA was significantly higher for lesions with RES (46.2 ± 13%) than without RES (35.8 ± 12%), $p<0.001$. No other predictors of RES of individual lesions were identified.

Thus, the majority of pts with CR after PTCA of MV do not have multiple RES, and higher residual post-PTCA narrowing appears to predict lesion RES in pts with CR after PTCA of multiple vessels.

CLINICAL AND MORPHOLOGIC FACTORS IN PREDICTION OF RESTENOSIS AFTER MULTIPLE VESSEL ANGIOPLASTY

Richard E. Shaw, Ph.D., Richard K. Myler, M.D. F.A.C.C., Jodi Fishman-Rosen, R.N., M.S., Mary C. Murphy, R.N., M.S., Simon H. Stertzer, M.D., F.A.C.C., Eric J. Topol, M.D., San Francisco Heart Institute, Daly City, CA

In patients undergoing angioplasty (PTCA) in multiple coronary vessels, we tested the hypothesis that clinical factors are more likely to predict restenosis in patients in whom all lesions recur (ALR) and that morphologic factors are more predictive of restenosis in patients in whom only some lesions recur (SLR). Angiographic followup was obtained in 97 patients who underwent successful multiple vessel PTCA. The clinical factors evaluated were: sex, age, smoking, rest/nocturnal angina, anginal class, angina duration (AD), cholesterol, hypertension and diabetes. The morphologic factors assessed were: percent diameter stenosis (PDS) and pressure gradients pre- and post-PTCA, and balloon inflation pressure (BIP). Univariate and multivariate logistic regression showed that compared to patients in whom all lesions were patent: 1) the ALR group was more likely to have diabetes ($p<.05$), higher levels of cholesterol ($p<.01$), were current smokers ($p<.01$), and had shorter AD ($p<.05$); and 2) the SLR group was more likely to have higher PDS pre-PTCA ($p<.05$), required higher BIP ($p<.05$), and had shorter AD ($p<.05$). Thus, it appears that clinical and morphologic factors may be related to different patterns of restenosis in patients undergoing multiple vessel PTCA.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #260/261
Technological Aspects of Coronary Angioplasty

A NEW R - WAVE - TRIGGERED CORONARY ANGIOPLASTY CATHETER SYSTEM ALLOWS PROLONGED DILATATION TIME WITH PHYSIOLOGICAL PERFUSION DURING DILATATION.

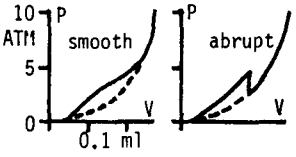
Adolf Kuhl, M.D., Gerd-H. Reil, M.D. and Paul R. Lichtlen, M.D., F.A.C.C., Medical School Hannover, Federal Republic of Germany.

We developed a new modified GRÜNTZIG coronary angioplasty catheter system which allows very fast inflation (40 ms) and deflation (60 ms) of the balloon. This enables R - wave - triggered inflation only during systole and a part of diastole and continues coronary perfusion, if deflation time is long enough. We studied 8 dogs (thoracotomy, magnetic flowmeter LAD or RCX, coronary angiography) by varying occlusion time from 150ms up to 80% RR - interval (flow zero). Maximum dilatation time was 5 minutes. Coronary mean flow (25 ± 15 ml) did not change significantly during inflation up to 30% RR - interval (systolic duration), and decreased only up to 50% if the inflation time was approximately 80% of the RR-interval. Coronary peak flow increased from 52 ± 32 ml (balloon deflated) to 110 ± 50 ml (occlusion time 50% of RR - interval).
During 5 minutes of triggered dilatation within occlusion times lower than 80% of RR - interval we saw no ischaemic ECG changes and no reactive hyperaemia, a proof of sufficient coronary perfusion. This new coronary angioplasty catheter system allows physiological perfusion during the entire procedure and thereby a marked prolongation (10 minutes tested) of dilatation. It is the hope that in this way the technique becomes safer, i.e. less arterial injury occurs and ischaemia is reduced during procedure.

QUANTITATIVE ASSESSMENT OF LESION DILATATION DURING CORONARY ANGIOPLASTY IN MAN.

Linda L. Demer, M.D., Ph.D., Avanindra Jain, M.D., Craig J. Hartley, Ph.D., Albert E. Raizner, M.D., F.A.C.C., John M. Lewis, M.D., F.A.C.C., and Robert Roberts, M.D., F.A.C.C., Baylor College of Medicine, Houston, TX.

To assess the mechanism and quantify the extent of dilatation during coronary angioplasty, we instrumented the inflation syringe to measure the pressure (P) and volume (V) within the balloon. P was plotted vs V during inflation on an X-Y storage oscilloscope before insertion (control) to determine balloon properties, and during each inflation in 39 patients. Compared to control, P began to rise at lower V within the lesion until the lesion no longer impeded the balloon and above that pressure the curve superimposed on control. With subsequent inflations (2-4) the curves met at progressively lower pressures until they superimposed over the entire pressure range suggesting complete dilatation of the lesion. In 32 patients, 7 of whom had calcified lesions, the curves were smooth and the first inflation intercepted control at 5 ATM (range 3 to 8). In 7 patients, none of whom had calcified lesions, an abrupt drop in P was noted during inflation suggestive of cracking. Six of these patients had angiographic evidence of dissection compared to 1 in the other group. We conclude that balloon P-V measurements demonstrate the minimum pressure and the number of inflations required to dilate the lesion and can be used to detect "cracking" associated with dissection. Thus, monitoring of dilatation by this method should reduce the number of unnecessary inflations, lower the maximum pressure applied, and help to anticipate complications.



SYNCHRONIZED CORONARY SINUS RETROPERFUSION (SCSR)DURING LAD ANGIOPLASTY - Bonnie H. Weiner, MD, FACC, Joel M. Gore, MD, Kathy M. Sloan, BSN, Joseph R. Benotti, MD, FACC, John MJ. Gaca, MD, Okike N. Okike, MD, Thomas J. VanderSalm, MD, Steven P. Ball, RN, Jeanne Corrao, BSN, Joseph S. Alpert, MD, FACC, James E. Dalen, MD, FACC. UMass Medical School, Worcester, MA

To determine the benefit of SCSR during acute anterior ischemia, 3 patients (pts) undergoing elective LAD PTCA were evaluated. Following 2 initial balloon inflations, SCSR was instituted by inserting 8F catheters into the femoral artery and coronary sinus (CS). Oxygenated blood is withdrawn from the femoral artery and is infused in an ECG synchronized manner during diastole through the CS catheter. This catheter consists of an autoinflatable balloon allowing temporary CS occlusion and an end hole for blood delivery. After 15 minutes of SCSR, 2 additional inflations were performed. SCSR was then discontinued and further inflations performed as necessary. During all inflations, right heart pressures, transtenotic gradient, chest pain, and 12 lead ECG were recorded. With SCSR the time to the onset of chest pain increased from 28.3±20.9 sec to 99.7±58.0 secs. ($p<.05$). Compared to no SCSR, the time necessary for the development of comparable degrees of ST elevation increased from 60 sec to 137.3±31.5 sec ($p<.05$). During balloon occlusions, there were no differences in the transtenotic gradient or right heart pressures before, during or after SCSR. Conclusion: SCSR is effective in delaying the development of chest pain and ECG changes during LAD PTCA. This may allow for a safer approach to more complicated disease. Moreover, with the aid of SCSR, it may be possible to study the role of longer balloon inflations in decreasing the incidence of restenosis.

AUTOMATED QUANTITATIVE ANALYSIS OF STENOSES DURING PTCA

Richard W. Smalling, M.D., Ph.D., FACC, Richard L. Kirkeeide, Ph.D., Linda Parsel, Akira Nishikawa, M.D., Robert D. Ekas, Ph.D., and K. Lance Gould, M.D. University of Texas Medical School at Houston, Houston, Texas.

Quantitative analysis of 18 stenoses subjected to percutaneous coronary angioplasty (PTCA) were performed with orthogonal angiography utilizing densitometry and border detection with an automated computer program. The program determined normal vessel as well as stenosis diameter and cross sectional area, % diameter and area reduction, calculated coronary flow reserve and transstenotic pressure gradient. Transstenotic pressure gradients (DP) were measured pre and post PTCA. Stenosis severity (SS) was estimated by two experienced angiographers. There was no correlation between the measured value of SS (64 ± 15%) and the estimated SS (85 ± 8.8%) pre PTCA or post PCA, (43 ± 13 vs. 33 ± 7%). There was no correlation between % improvement in minimum coronary diameter (D) and % improvement in measured DP. There was a poor correlation between improvement in minimum stenosis D and improvement in calculated coronary flow reserve (CFR) (R = .42). CFR did increase significantly from 2.5 ± 1.3 to 4.10 ± .4 (P<.005) post PTCA. There was a substantial decrease in normal vessel D adjacent to the stenosis (3.26 ± .64 to 2.98 ± .59 mm, P < .025) post PTCA which may adversely affect estimates of PTCA success using geometrical techniques. Since stenoses with CFR > 3.5 are not physiologically significant, CFR may be a more useful end point for PTCA than simple geometric appearance (% diameter reduction) or transstenotic pressure gradient.

ASPIRIN AND DIPYRIDAMOLE PRETREATMENT IN THE PREVENTION OF ACUTE THROMBUS FORMATION DURING CORONARY ANGIOPLASTY.

Elliot Barnathan, MD, Warren K. Laskey, MD, FACC, J. Patrick Kleaveland, MD, FACC, William G. Kussmaul, MD, John W. Hirshfeld, Jr., MD, FACC, University of Pennsylvania, Philadelphia, PA.

To assess the efficacy of pretreatment with aspirin (ASA) and/or dipyridamole (DP) in the prevention of acute coronary thrombus formation during coronary angioplasty (PTCA), we reviewed films, blinded to treatment group, and hospital records of 300 consecutive initially successful PTCA's. Films before PTCA, immediately and 30 min after the last balloon inflation were assessed for the presence of any thrombus. Thirty-seven patients who received streptokinase or had 100% stenosis or thrombus on pre-PTCA films were excluded. Group A received no ASA or DP while Groups B, C, and D received therapy either preadmission, or within 24 hrs of PTCA, or both. Group D' (subgroup of Group D) received ASA and DP both preadmission and within 24 hrs of the PTCA. The results listed below indicate those PTCA's in which a definite thrombus was visible on either the immediate or 30 min post-PTCA films. Fourteen of 39 post-PTCA thrombi were considered to be clinically significant (100% occlusion, requiring streptokinase, or emergency coronary artery bypass grafting).

Group	# With Any Thrombus		p vs A	Clinically Significant		p vs A
A (control)	22/101	(21.8%)		12/101	(11.9%)	
B (DP alone)	4/20	(20.0%)	NS	0/20	(0%)	NS
C (ASA alone)	4/32	(12.5%)	NS	1/32	(3.1%)	NS
D (ASA/DP)	9/110	(8.2%)	.01	1/110	(0.9%)	.002
D'(max ASA/DP)	0/32	(0%)	.009	0/32	(0%)	.09

Thus, antiplatelet therapy with ASA and DP prior to PTCA decreases the incidence and clinical significance of acute coronary thrombus formation.

PULSED LASER ANGIOPLASTY: DESIGN CRITERIA FOR CLINICAL APPLICATION. Frank Litvack, M.D., Warren Grundfest, M.D., Tsvi Goldenberg, Ph.D., Todd Sherman,M.D., Stuart McDermid, Ph.D., James Margitan, Ph.D., Tom Pacala, Ph.D., James Laudenslager, Ph.D., James Forrester, M.D., FACC, Cedars-Sinai Medical Center and Jet Propulsion Laboratory, Los Angeles and Pasadena, CA.

Pulsed laser angioplasty requires the delivered energy to be sufficient to ablate calcified plaque, yet not destroy the transmitting fiberoptic. We defined the energy requirements for tissue ablation through air by irradiating 727 segments of human cadaver aorta with a Q switched Nd:YAG (532,355 and 266 nm) and a magnetically switched excimer laser (308 nm). Energy density (ED) was varied from 9-120 mJ/mm^2. Ablation threshold (AT) was defined as minimum energy required to create a 1 mm crater with 2,000 pulses.

Results:

λ	pulse	Hz	AT	vs. calcified plaque
532 nm	7 nsec	10	70 mJ/mm^2	no
355 nm	7 nsec	10	15 mJ/mm^2	Yes
266 nm	10 nsec	10	<9mJ/mm^2	Yes
308 nm	40,150 nsec	10,30	5 mJ/mm^2	Yes

As ED increased, the number of pulses required to perforate (PP) a segment decreased asymptotically to a minimum required number (min PP). The energy level between AT and min PP, therefore, define the cutting range for each laser. Fiberoptics were destroyed by 10 nsec pulses at AT energies but 150 nsec excimer energy sufficient to ablate densely calcified plaque was transmitted through a 0.6 mm o.d., 6 meter long fiber. Conclusions: 1. AT for plaque is an order of magnitude lower in the ultraviolet than in the visible. 2. Pulsed laser ablation via fiberoptics requires low AT and long pulses and as such the magnetically switched excimer is the best available pulsed power source for laser angioplasty.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #360–361
Thrombolysis III

PRESERVATION OF VENTRICULAR FUNCTION WITH VERY EARLY INTRAVENOUS STREPTOKINASE THERAPY IN ACUTE ANTERIOR MYOCARDIAL INFARCTION.

Mervyn S. Gotsman, M.D., F.R.C.P., F.A.C.C., David G. Fine, M.D., Sima Welber, B.Sc., Dan Sapoznikov, Ph.D., Chaim Lotan, M.D., Gideon Koren, M.D., Yonathan Hasin, M.D., Avraham T. Weiss, M.D., David Applebaum, M.D.
Hadassah University Hospital, Jerusalem, Israel.

The effect of myocardial salvage after intravenous thrombolysis in acute myocardial infarction (AMI) is still being debated. We examined the importance of time to administration of intravenous streptokinase (IVSK) on cardiac function. We administered 750,000 units of IVSK to 29 consecutive patients with anterior AMI within four hours of the onset of chest pain, who had no evidence of previous AMI. Infarct size in each patient was assessed six days after AMI using coronary angiography to calculate global ejection fraction (GEF) and anterior regional ejection fraction (REFA), and ECG to calculate an infarct score (SCOR). All 10 patients receiving IVSK more than two hours after onset of pain had significantly abnormal GEF, REFA, and SCOR, compared to only about one-third of the 19 patients receiving it in less than two hours.

	Time to IVSK <2 hrs.	Time to IVSK 2-4 hrs.	P Value
GEF >55%	12/19	0/10	0.001
REFA >55%	14/19	0/10	0.0001
SCOR <8	13/17	0/10	0.0001

We conclude that if thrombolytic therapy is delayed greater that two hours after the onset of pain in anterior AMI significant damage has occured. Conversely, early IVSK (less than two hours) is associated with preservation of myocardial function.

INTRAVENOUS STREPTOKINASE (STK) IN RURAL COMMUNITY HOSPITALS WITH SUBSEQUENT TRANSFER FOR TERTIARY CARE: SAFETY AND EFFICACY OF A STRATIFIED APPROACH TO ACUTE MYOCARDIAL INFARCTION (AMI). Douglas G. Wysham, MD, Douglas R. Salmon, MD, Wayne N. Leimbach, MD, Dave A. Buchanan, MD, Robert F. Wilson, MD, J. Michael Kioschos, MD, Maryl R. Johnson, MD, FACC, Philip E. Aylward, MD, Peter T. Kirchner, MD, Melvin L. Marcus, MD, FACC, Carl W. White, MD, FACC. CV Center, University of Iowa, Iowa City, IA.

To maximize benefits from thrombolytic therapy in AMI, treatment must be begun early, and care continued where sophisticated diagnostic and interventional facilities are available. To determine if IV STK given in small rural hospitals followed by transfer for tertiary care was safe and could decrease the time to STK treatment, we prospectively studied 31 consecutive patients (pts.) with AMI. Nineteen received IV STK locally and were transferred by helicopter using flight nurses trained in defibrillation. Twelve pts. were similarly transferred and IV STK was begun in our ER. Mean time from pain to IV STK was 3±.2 hr. (vs. 5.3±.5 using IC STK in our previous study: AJC 54:705,1984) p<.05. Importantly no complications occurred in transfer. On arrival patients were stratified for further therapy based on an isotope ejection fraction (EF); acute angiography was performed only in pts. with immediate EF <50% (18/31). Antegrade flow was present in 11/18 (61%). Further IC STK reperfused 3/6 totally occluded arteries, but no angiographic improvement in flow was seen in those subtotally stenosed. Final patency was 14/18 (78%). CONCLUSIONS: In a rural setting, IV STK significantly decreases time to treatment when compared to IC STK. Immediate transfer after IV administration of STK can be accomplished safely and subsequent sophisticated care is not precluded. Additional IC STK, however, adds only modestly to the efficacy of thrombolysis.

PREVALENCE OF RECURRENT ISCHEMIA FOLLOWING THROMBOLYTIC THERAPY IN A COHORT OF SINGLE VESSEL DISEASE PATIENTS.

David H. Schaer, MD, Alan G. Wasserman, MD, FACC, Roy H. Leiboff, MD, FACC, Lisa Martin, MD, Richard J. Katz, MD, FACC, George B. Bren, MD, P. Jacob Varghese, MD, FACC, Allan M. Ross, MD, FACC, George Washington University, Washington, DC.

Analysis of follow-up data to assess the risk of recurrent angina or reinfarction ("ischemic double jeopardy") in patients receiving thrombolytic therapy is confounded by events potentially secondary to disease in a non-infarct artery. We therefore determined the prevalence of recurrent ischemic events over a 12 month follow-up in all 40 single vessel disease infarct patients managed within larger thrombolytic trials. All pts had angiography <5 hrs from symptom onset. Outcome analysis was based upon infarct artery patency (PAT), either spontaneous or with pharmacologically induced reperfusion (19 pts), or occlusion (OCC) (21 pts) 90 minutes after the start of angiography. One year mortality was low in both groups, 1/19 (5%) PAT; 2/21 (9.5%) OCC. There was no significant difference in resting ejection fraction of the OCC or PAT groups (49%±10 vs 47%±13). Recurrent angina during the follow-up year occurred in 10/19 (53%) of PAT pts but only 1/21 (5%) in the OCC group, p<.01. Recurrent infarction was seen in 3/19 (16%) in the PAT group and 1/21 (5%) in the OCC group (p=ns). Combining both endpoints, angina or reinfarct, recurrent ischemia occurred in 13/19 PAT pts (68%) and 2/21 OCC pts (10%), p<.001. Conclusion: Examination of this cohort confirms that single vessel infarct patients are at low risk for further ischemic events unless they have successful reperfusion. Further therapeutic strategies (i.e. PTCA) must be developed to reduce the risk of "ischemic double jeopardy" in such patients.

THE SERUM LEVEL OF D DIMER, A DEGRADATION PRODUCT OF CROSSLINKED FIBRIN, IS ELEVATED FOLLOWING INTRAVENOUS STREPTOKINASE BUT NOT FOLLOWING CONVENTIONAL MANAGEMENT IN ACUTE MYOCARDIAL INFARCTION.

Allan S. Lew MD, Linda Berberian MT, ASCP, Bojan Cercek MD, Pierre Laramee MD, Stephen Lee MD, Hanoch Hod MD, P.K. Shah MD, FACC and William Ganz MD, CSc, FACC. Cedars-Sinai Medical Center, Los Angeles CA.

D dimer, a degradation product of crosslinked fibrin, is generated by fibrinolysis but not by fibrinogenolysis and can be reliably detected by specific monoclonal antibody techniques. We studied the effect of high-dose IV streptokinase (SK) in acute myocardial infarction on the serum level of D dimer. Twenty patients with acute transmural myocardial infarction of less than 3 hours duration were studied using a semi-quantitative monoclonal antibody latex agglutination assay. No patient had an elevated D dimer on admission. Fourteen patients received IV-SK and 6 patients were treated conventionally. Of the 14 IV-SK patients, an elevated serum level of D dimer was detected within 1 hour of streptokinase administration in 12 Pts and within 4 hours in the remaining 2 patients. Elevated D dimer persisted for more than 10 hrs in all 13 patients in whom reperfusion was achieved but in the one patient without reperfusion, elevated D dimer was only briefly detectable for a 2 hour period following streptokinase. In contrast, no D dimer was detected during the first 24 hours in any of the 6 conventionally treated patients including 2 patients manifesting the clinical syndrome of 'spontaneous reperfusion'.
Our data suggest that: 1) Coronary thrombolysis by IV streptokinase generates the crosslinked-fibrin degradation product, D dimer but 2) No detectable spontaneous fibrinolysis occurs in conventionally treated patients with acute myocardial infarction, including patients with the clinical syndrome of 'spontaneous reperfusion'.

INTRAVENOUS UROKINASE IN ACUTE MYOCARDIAL INFARCTION: ACUTE AND LATE EFFECTS ON LEFT VENTRICULAR THROMBUS FORMATION

Peter Kremer, Wolfgang Aschenberg, Joachim Schofer, Detlef G. Mathey. Dept. of Cardiology, University Hospital Eppendorf, Hamburg, West Germany

To determine whether intravenous urokinase in acute myocardial infarction (MI)reduces the acute and late ventricular thrombus (LVT) formation we performed two-dimensional echo at 3-4 weeks and 6 mondths after MI in patients (pts) allocated to i.v. urokinase (U,n=96) or conventional treatment (C,n=74). In U pts coronary patency was achieved in 60% one hour after a bolus injection of 2 x 10^6 units urokinase. There were no differences concerning infarct location or anticoagulant therapy after MI in both groups. Echoes were blindly interpreted for LVT and aneurysm (A) formation by two observers.

	3-4 weeks after MI		6 months after MI	
	C	U	C	U
LV thrombus	11 %	1 %*	9 %	2 %*
LV aneurysm	16 %	17 %	16 %	18 %

*p < 0.01 (C vs.U)

Despite the similar prevalence of aneurysm formation in both groups the incidence of LVT was significantly lower in U pts at follow-up. We conclude that i.v. thrombolysis with urokinase in acute MI results in a significant reduction of LV thrombus formation as compared to conventional treatment.

ACUTE NON-Q WAVE INFARCTION ASSOCIATED WITH EARLY ST SEGMENT ELEVATION: EVIDENCE OF SPONTANEOUS REPERFUSION AND IMPLICATIONS FOR THROMBOLYTIC TRIALS. Barry L. Huey MD, George A. Beller MD, FACC, Mihai Georghiade MD, FACC, Thomas W. Nygaard MD, FACC, Denny D. Watson PhD, Robert S. Gibson MD. Univ. of Virginia, Charlottesville, Virginia

Of 241 consecutive patients (pts) with MB-CK confirmed acute uncomplicated MI, 162 (67%) had ≥1mm ST segment ↑ on the admission ECG. None received thrombolytic therapy or acute angioplasty. Predischarge angiography, radionuclide ventriculography and exercise Tl-201 scintigraphy were performed 10±3d post-MI. Based on serial ECGs (days 1,2,3 and 10), all 162 infarcts were classified as Q ([QMI], n=120[74%]) or non-Q wave ([NQMI],n=42[26%]). These 2 groups were similar with respect to the extent and distribution of angiographic CAD and time from onset of symptoms to admission (4.5 vs 4.9hrs,p=NS). Although QMI pts exhibited greater ST↑, the amount observed in the NQMI group was appreciable: ST↑ per lead (2.3 vs 1.7 mm,p<.01), # leads with ST↑≥1mm (3.7 vs 2.8,p<.01), and ΣST↑ (9.3 vs 5.4 mm,p<.01). When compared to QMI, the NQMI pts had shorter time to peak CK (21.8 vs 14.9 hrs,p<.01) and a higher infarct vessel patency rate (24% vs 57%,p<.01) as well as lower peak CK values based on 4 hr sampling (1331 vs 662, p<.01), higher LVEF (45 vs 52%,p<.01) despite a greater prevalence of prior MI (9 vs 29%,p<.01), fewer LV segments with akinesis (2.2 vs 1.1,p<.01) and fewer persistent Tl-201 defects (2.1 vs 1.3,p<.01). Thus, the pathogenesis of NQMI in some pts may involve spontaneous reperfusion characterized by early peaking CK and a high prevalence of patent infarct vessels which results in better LV function and regional perfusion. These results may have implications in the design of thrombolytic trials since 26% of pts with early ST↑ evolved NQMI with a late infarct vessel patency rate approaching that seen in pts treated with thrombolytic agents.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #360/361
Myocardial Infarction—Clinical: Prognosis

CLINICAL IMPORTANCE OF EARLY ISCHEMIA AFTER ACUTE MYOCARDIAL INFARCTION (AMI)
Pierre Théroux, M.D, F.A.C.C., Xavier Bosch, M.D, Guy B. Pelletier, M.D, F.A.C.C, David D. Waters, M.D, F.A.C.C., Simon Kouz, M.D., Denis Roy, M.D, Montreal Heart Institute, Montreal, Canada

Early ischemia defined as angina with transient ST-T changes during hospitalization, 24 hours or more after an AMI was observed in 79 (17.6%) of a consecutive series of 449 pts surviving an AMI and catheterized a mean of 10±3 days after admission. Clinical factors significantly associated with ischemia were: no. of risk factors (1.6±.7 vs 1.4±.7/pt, p=.01), duration of heart disease (38±50 vs 24±46 mo., p=.02), previous angina (53 vs 31% of pts, p<.0005) or MI (34 vs 20%, p<.01), a non Q-wave AMI (52 vs 32%, p<.001) and lower peak CK value (1280±1121 vs 1818±1581 IU/L, p<.001). Age, sex, site of MI were not significant. The angiographic correlates were no. of ≥70% stenosed vessels (2.1±.8 vs 1.7±.8/pt, p<.0001), no. of diseased coronary segments (2.8±1.4 vs 2.1±1.2, p<.0001), left anterior descending coronary involvement (77% vs 62% of pts, p=.01), Friesinger score (10±2.8 vs 8±2.8, p<.0001), Gensini score (58±32 vs 41±29, p<.0001), no. of normal contractile segments jeopardized by coronary stenosis (1.9±1.3 vs 1.3±1.1/pt, p<.0002), and fewer collateral vessels (54 vs 64% of pts, p=.04). The % stenosis of the infarct-related vessel, the ejection fraction and the contractile score of the infarct area were the same. Stepwise logistic regression retained 3 independent predictors of early ischemia: no. of diseased vessels, presence of non Q wave AMI and history of previous angina.
During hospitalization, 22 of 79 pts with ischemia (28%) experienced MI extension vs 9 of 370 others (2.4%, p<.0001). During a mean follow-up of 14±8 mo. (2 to 28), the cumulative % survival was 83% in pts with early ischemia and 91% in those without (p=.01); survival without MI was 67% vs 80% (p<.001) and survival without cardiac events (death, MI, unstable angina, bypass surgery) 39% vs 65% (p<.00001).
Thus early ischemia after AMI is a frequent finding associated with more severe coronary artery disease and identifies a high risk group for MI extension in-hospital and cardiac events during follow-up.

PREDICTION OF LATE SUSTAINED VENTRICULAR TACHYARRHYTHMIAS AFTER MYOCARDIAL INFARCTION

Hosen Kiat MB, David Richards MD, David Ross MB, FACC, John Uther MD. Westmead Hospital, NSW Australia.

568 clinically well patients (pts) aged 28-76 years underwent right ventricular programmed electrical stimulation with a standardised protocol 6-28 days after acute myocardial infarction (AMI). Sustained ($\geq$ 10 sec) ventricular tachycardia (VT) was inducible in 97 (17%) pts. Pts with and without inducible VT were similar in terms of age, coronary anatomy, left ventricular ejection fraction, results of ambulatory ECG monitoring and exercise testing. All pts were followed for 12 months. Spontaneous ventricular tachyarrhythmias (witnessed instantaneous death, documented sustained VT or ventricular fibrillation (VF)) occurred during follow up in 21 of 97 (22%) pts with inducible VT and 10 of 471(2%) pts without inducible VT ($p<0.0005$). Spontaneous ventricular tachyarrythmias during follow up in the pts with inducible VT were associated with anterior infarction (71% vs 31%, $p<0.001$), longer cycle length of induced VT (250 ± 60 vs 210 ± 32 msec, $p< 0.001$), and VT induction with a single extrastimulus (14% vs 1%, $p < 0.01$).
We conclude: 1. Inducible VT following AMI was a strong predictor of sustained ventricular tachyarrhythmias in the first year after AMI. 2. Non-electrophysiologic variables did not predict ventricular tachyarrhythmias. 3. The power of prediction by programmed stimulation of late sustained ventricular tachyarrhythmias may be increased by consideration of the site of infarction, ease of VT induction and cycle length of induced VT.

OVERVIEW OF MORTALITY RESULTS FROM ALL RANDOMIZED CONTROLLED TRIALS OF EARLY IV BETA-BLOCKADE AFTER MYOCARDIAL INFARCTION

ISIS Collaborative Group, Radcliffe Infirmary, Oxford, England (Chairman P.Sleight, D.M., F.R.C.P., Statistician R.Peto, M.A., M.Sc., Co-ordinator R.Collins, M.B. B.S., M.Sc.)

Analysis for mortality during days 0-7 in all randomized trials of early IV beta-blockade following myocardial infarction. The number of deaths Observed in the treatment group of a particular trial minus the number Expected in that same trial if treatment had no effect on mortality (O-E) is tabulated:

TRIALS	O-E (in treated patients)	VARIANCE OF (O-E)	% REDUCTION IN MORTALITY (± SE)
25 small trials (238 deaths/5531)	-0.1	55.9	0 ± 12
"MIAMI" trial (172 deaths/5778)	-6.6	41.7	14 ± 14
"ISIS" trial (672 deaths/16048)	-25.9	161.0	15 ± 7
All IV trials	-32.6	256.6	12 ± 6

These results suggest that treatment of about 150 patients with early intravenous beta-blocker, followed by one week of oral treatment, would on average save about one life.

LIMITATION OF INFARCT SIZE AND REDUCTION OF LATE VENTRICULAR ARRYTHMIAS WITH EARLY ADMINISTERED TIMOLOL IN ACUTE MYOCARDIAL INFARCTION: A ONE-MONTH FOLLOW UP STUDY.

Fernando Roqué, MD for the TIARA Group Investigators, Clínica Olivos, Maipú 1660, 1638 Buenos Aires, Argentina.

Results of experimental and clinical studies suggest that the early administration of the beta-blocker timolol (T) limits infarct size. However, this action has not been demonstrated using CKMB, a specific marker of ischemic damage, and the effect of early T on late ventricular arrythmias (LVA) has not been clearly established.

To provide such information, 13 clinical centers randomized 200 patients (pts) out of 2094 consecutively screened within 6 hr of onset of chest pain of at least 30 min duration. The 102 pts in the placebo group (P) were comparable at baseline to the 98 pts given T. Patients initially received 5.5 mg T iv, followed by oral T (10 mg bid) for 28 days. Infarct size was determined by serial analysis of serum CKMB while LVAs were studied by Holter monitoring (HM) on days 7, 14, 21 and 28. Results were analyzed according to the intention to treat approach. In comparison with P, T reduced significantly the cumulative release of CKMB (137.6 IU/l vs 106.0 IU/l; $p < 0.01$) and the peak serum activity of the enzyme (98.6 IU/l vs 76.3 IU/l; $p < 0.01$). The 552 HM of 162 pts, showed that ventricular tachycardias occurred in 7 pts of the T group and in 16 pts in the P group ($p < 0.05$). The severity of ventricular arrythmias, when scored according to Lown, was lower in the T group; a difference that was significant on day 14 ($p < 0.01$). Ten pts in the T group and 18 receiving P developed left ventricular failure ($p > 0.05$). Three patients died in the T group and 7 in the P group.

In conclusion, the beta-blocker timolol given iv within 6 hr of the onset of infarction and then orally for 28 days, reduces infarct size as measured by CKMB as well as the incidence and severity of late ventricular arrythmias.

MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION IN THE MULTI-CENTER POST INFARCTION PROGRAM.

Frank I. Marcus, M.D., F.A.C.C., Leonard Cobb, M.D., F.A.C.C., Jesse Edwards, M.D., F.A.C.C., Lewis Kuller, M.D., F.A.C.C., Ruth Serokman and the Multi-Center Post Infarction Research Group; University of Arizona, Tucson.

We enrolled 867 patients (pts) in a prospective study to determine prognostic factors in pts surviving the coronary care unit phase of acute myocardial infarction (MI). During a mean of 22 months of follow-up, 101 pts died. The circumstances of death were carefully examined in order to define the cause, mechanisms, time of occurrence in relation to mechanism and presence of ischemia in the terminal event. A classification proposed by Hinkle and Thaler was used to define the mechanism of cardiac death and the presence of ischemia. Results: 77 deaths were due to cardiac causes; of these 75% were arrhythmic. Neither the frequency of an ejection fraction 40% at discharge nor the presence of VEDs 10/hr or pairs or runs were different in pts who died of myocardial failure versus those who died an arrhythmic death. The time between the onset of new symptoms and death occurred in less than 1 hr in 23 pts who had an arrhythmic death and 1 pt who had a circulatory death. However, when death occurred more than 1 hr after onset of new symptoms, 50% had an arrhythmic mechanism. Ischemia preceded the terminal event in 66% of 38 pts with a witnessed arrhythmic death and in 63% of 18 pts whose witnessed death was due to myocardial failure. Conclusion: This study emphasizes the high incidence of ischemia preceding the terminal event. This finding may influence strategies to decrease mortality after an MI. The definition of sudden death as occurring within 1 hr of onset of symptoms was specific for an arrhythmic death but the definition of sudden death as within 24 hrs was not useful in defining the mechanism of death.

PROPHYLACTIC THERAPY WITH DILTIAZEM PREVENTS EARLY REINFARCTION: A MULTICENTERED RANDOMIZED DOUBLE-BLIND TRIAL IN PATIENTS RECOVERING FROM NON-Q-WAVE INFARCTION. R Roberts, MD, FACC, RS Gibson, MD, WE Boden, MD, FACC, P Theroux, MD, FACC, HD Strauss, MD, FACC, CM Pratt, MD, FACC, M Gheorghiade, MD, FACC, RJ Capone, MD, FACC, MH Crawford, MD, FACC, RC Schlant MD, FACC, RE Kleiger, MD, FACC, MB Perryman, PhD, and the DRS Group.

Patients (pts) recovering from non-Q-wave infarction are recognized to be prone to repetitive episodes of reinfarction, resulting in a long-term prognosis similar to Q-wave infarction despite their benign course acutely. A randomized double-blind study of 576 pts with non-Q-wave infarction was performed, 287 receiving diltiazem (D) and 289 placebo (P), involving 9 universities, 7 in the U.S. and 2 in Canada. Pts were randomized 24-72 hours after onset of infarction, manifested by appropriate symptoms without Q-waves and confirmed by elevated plasma MBCK. Diltiazem, 360 mg/day, or P was given for up to 14 days. The primary endpoint was reinfarction, defined as a secondary elevation in plasma MBCK. MBCK was analyzed by a central core lab as were the ECGs and the study overseen by an independent policy board. Mean duration of therapy (10.5 days) was identical for P and D, as were baseline characteristics, including previous MI, age, and sex. Beta-blockade usage was similar being 51% in D and 56% in P. Due to adverse drug effects, 14 pts (4.8%) withdrew from D and 3 pts (1%) from P. The 14-day mortality (99% follow-up) was similar with 9 deaths in P and 11 in D. Reinfarction occurred in 41 pts, 26 in P and 15 in D, which is a difference of 42% ($p<.04$). Withdrawal for angina occurred in 11 pts receiving D and 21 receiving P, a difference of 48% ($p<.04$). These results indicate diltiazem was well tolerated, safe, and effective in both the prevention of early recurrent infarction and angina occurring in patients after non-Q-wave infarction.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #366/367
Treatment of Pulmonary Embolism, Pulmonary Hypertension and Cor Pulmonale

EFFICACY AND SAFETY OF TISSUE PLASMINOGEN ACTIVATOR IN THE TREATMENT OF ACUTE PULMONARY EMBOLISM.
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Current management of pulmonary embolism (PE) relies on heparin (for secondary prevention) and rarely utilizes lytic therapy for primary dissolution of clot, due to fear of major bleeding complications. Therefore, we assessed the efficacy and safety of a new lytic agent, recombinant human tissue-type plasminogen activator (rt-PA) in the treatment of PE. Patients were excluded if they had symptoms of PE more than 5 days, active bleeding, or if they had been operated upon within the prior week. After establishing the diagnosis of PE angiographically in 7 patients (4 postoperative and 3 medical), we administered rt-PA by continuous intravenous infusion (50 mg over 2 hours) and repeated the angiograms immediately thereafter. Each set of angiograms was reviewed by at least 3 investigators. In 5 patients, significant clot lysis occurred at 2 hours. Of the 2 remaining patients, 1 received an additional 40 mg of rt-PA over 4 hours and demonstrated marked clot lysis at repeat angiogram immediately thereafter. The other patient showed improvement on lung scan 4 hours after the 2-hour rt-PA infusion. Although minor skin oozing from venipuncture and arterial blood gas sites was common, no patient experienced major bleeding. Thus, in this initial pilot study among carefully selected patients, rt-PA appeared to be efficacious and safe in the rapid lysis of PE.

COMPARATIVE CARDIODEPRESSANT EFFECTS OF NIFEDIPINE AND DILTIAZEM ON RIGHT VENTRICULAR FUNCTION IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION. Milton Packer MD, FACC, Wai Hung Lee MD, Norma Medina RN, Madeline Yushak RN, Paul Kessler MD. Mount Sinai School of Medicine, New York, NY

Calcium antagonists have been advocated as pulmonary vasodilators in primary pulmonary hypertension (PPH), but may worsen RV dysfunction by their negative inotropic effects; thus, these patients (pts) offer a model in which the cardiodepressant actions of these drugs can be compared. We studied 9 pts with PPH, who received nifedipine (NIF, 20 mg orally) and diltiazem (DTZ, 90 mg orally) in random order on alternate days. Stroke volume index (SVI, ml/beat/m^2), heart rate (HR, bpm), mean systemic arterial (BP), mean pulmonary arterial (PAm) & mean right atrial pressures (RA, mm Hg), systemic and pulmonary vascular resistances (SVR and PVR, d-s-c) and RV stroke work index (RW, g-m/m^2) were measured before (C) & at peak effect of each drug; * = $p<.05$ (C vs drug); † = $p<.05$ (NIF vs DTZ):

	SVI	HR	BP	PAm	RA	SVR	PVR	RW
C	24	90	80	56	12	1617	1218	14
NIF	24	102*	63*	46*	17*	923*	807*	10*
C	23	90	83	57	13	1815	1261	13
DTZ	27*†	84*†	76*†	49*	13†	1452*†	1035*†	14†

DTZ produced modest ↓ in PVR and SVR which resulted in small ↓ in PA and BP and ↑ in SVI. Although NIF produced greater ↓ in PVR and SVR than did DZ (both $p<.05$), SVI failed to ↑ with NIF, and thus, BP ↓ markedly followed by a reflex ↑ in HR (both $p<.05$ vs DTZ). This response could be explained by a negative inotropic effect exerted by NIF on the already compromised RV, since NIF caused a decline in RV performance (RW ↓ and RA ↑), whereas DTZ did not ($p<.05$ vs NIF). Three pts deteriorated clinically after NIF (severe dyspnea and hypotension), 2 of whom needed pressors for > 6 hrs; such events were not seen after DTZ.

In conclusion, despite greater ↓ in PVR, NIF exacerbates preexisting RV dysfunction in pts with PPH more than does DTZ.

NIFEDIPINE IN COR PULMONALE: HEMODYNAMIC PROFILE, ADVERSE EFFECTS AND LACK OF SUSTAINED HEMODYNAMIC IMPROVEMENT.
Sakti Mookherjee, M.D.,F.A.C.C.,Kumar Ashutosh, M.D., Milton Dunsky, M.D.,Norma Hill, RN, Harold Smulyan, M.D., F.A.C.C., Suman Vardan, M.D., Robert Warner, M.D. V.A. and Upstate Medical Centers, Syracuse, NY.

In 12 patients (pts) with Cor pulmonale (CP), resting hemodynamics were monitored pre and for 2 hours (hrs) post 20 mg sublingual nifedipine (N) and then q6 hrs for 24 hrs on N 20 mg orally. At 2 hrs the pulmonary vascular resistance (PVR) fell from 310±50 (SEM) to 236±36 ($p<0.02$) and the systemic vascular resistance (SVR) fell from 1645±139 to 1175±85 dyne sec/cm^5 ($p<0.001$), while the mean arterial pressure (MAP) fell from 97±5 to 83±4 mmHg ($p<0.005$). Cardiac output (CO-Fick) rose from 4.7±0.5 to 5.4±0.5 L/min ($p<0.005$), but mean pulmonary arterial (MPAP), PA wedge and right atrial pressures did not change. At 24 hrs MPAP fell from 31±3 to 25±2 mmHg ($p<0.05$) and PVR rose to 276±51 dyne sec/cm^5, albeit lower than control PVR ($p<0.05$), while CO returned to baseline. The fall in PVR was unrelated to control PaO_2 which fell from 60±3 to 55±2 torr ($p<0.05$). MAP fell further at 24 hrs to 76±3 mmHg ($p<0.01$) and SVR to 1163±99 dyne sec/cm^5. Right (RV) and left (LV) ventricular stroke work, radionuclide RV and LV ejection fractions (EF) and spirometry (SP) remained unchanged. Of 7 pts agreeing to participate in a repeat study after 6 weeks on same therapy, 3 were withdrawn for diarrhea, profound orthostasis and intractable edema respectively, and 1 was non-compliant. Three pts restudied after 6 weeks were subjectively unimproved and their initially reduced hemodynamic variables including MPAP and PVR returned to baseline. RVEF, LVEF and SP were unchanged, and mean PaO_2 remained low, 51 torr. Thus, N lowers MPAP and PVR in CP acutely, but has untoward side effects in many pts and is of doubtful benefit at the end of 6 weeks.

DILTIAZEM VS. DIGOXIN FOR HEART RATE CONTROL IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION.

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Diltiazem delays atrioventricular conduction & can be effective for heart rate(HR)control in patients(pts)with atrial fibrillation(AF). We compared the effects of digoxin(Dig)(serum concentration 1.4±0.3ng/ml) & diltiazem 240mg/day(DT240)& 360mg/day(DT360)alone & in combination on heart rate(HR)response in 12pts with chronic AF. HR was measured at rest,supine(Sup)& upright(Up),during submaximal(S Max)& maximal(Max)exercise(Ex)& 2 minutes post Ex(2min P Ex). HR(beat/min)was as follows: *p<0.05 vs Dig

	Sup	Up	S Max Ex	Max Ex	2min P Ex
Dig	86	101	154	170	116
Dig+DT240	69*	79*	114*	132*	90*
Dig+DT360	65*	70*	103*	121*	85*
DT240	88	107	140*	154*	113
DT360	79	86*	118*	136*	100*

DT360 alone was more effective than Dig at rest & Ex but resulted in complications in 75% of the pts necessitating reduction of dose to 240mg/day with resolution of side effects in most pts. DT240 was more effective than Dig during Ex but not at rest. Addition of DT to Dig resulted in enhancement of HR control at rest & Ex, the difference between Dig + DT240 & Dig + DT360 however was not statistically significant. 9 pts were maintained on Dig + DT240 for 15-40 days & showed persistent effects. CONCLUSIONS: DT 360mg alone is more effective than Dig for HR control in pts with AF, but associated with high incidence of side effects. The addition of DT 240 to Dig is safe & results in significant improvement of HR control at rest & during Ex in pts with chronic AF.

HEMODYNAMIC EFFECTS OF SIMULTANEOUS DOPAMINE AND DIGOXIN FOLLOWING CORONARY ARTERY BYPASS

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Sometimes impaired left ventricular performance occurs after coronary revascularization and vasodilators as well as inotropic agents have to be used.The aim of this study was to evaluate the effect of simultaneous administration of dopamine and digoxin on left ventricular function in the early postpump period. Investigations were performed in 8 open chest patients 3o to 1oo min. after discontinuation of cardiopulmonary bypass. Neasurements included left atrial pressure (LAP), mean aortic pressure (MAP), heart rate (HR) and cardiac output (CO) with the thermal dilution technique. From these parameters cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR) and the double product (DP) were calculated. Results are summarized in the table below. LAP was kept constant during all measurements.

	before digoxin			after digoxin		
	vase line	4 µg/kg/min	8 Dopamine	base line	4 µg/kg/min	8 Dopamine
HR	1o4	1o6	119*	94	98**	1oo**
MAP	8o	86*	95*	84	9o*	91*
SVI	33,4	47,1*	45,2*	37,1	41,2	49,2**
DP	11749	12922	16252	11998	13o3o*	14258**

* p < o,o5 from base line **p < o,o5 before/after digoxin

Simultaneous administration of dopamine and digoxin showed an increase of SVI and a significant lower increase of DP as compared with dopamine alone. It is concluded that in postoperative coronary patients the chronotropic effects of dopamine can be ameliorated with digoxin, which might have impact on myocardial oxygen consumption.

USE OF THE END-SYSTOLIC PRESSURE-DIMENSION RELATIONSHIP TO ASSESS INOTROPIC RESPONSE OF DIGOXIN IN NORMAL MAN.

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The inotropic dose-response curve of chronically administered digoxin in normal humans is not known. The end-systolic pressure (ESP)-end-systolic dimension (ESD) relationship is a sensitive load-independent index of left ventricular contractility, and can be assessed using echocardiography, cuff blood pressure, and calibrated carotid pulse tracings. We used this methodology to assess the effect of digoxin on LV contractility in 9 normal volunteers to whom oral digoxin was administered for at least 8 days in both low-dose (LD) and high-dose (HD) regimens. Mean serum digoxin (D) levels were 0.9 ± 0.1 ng/ml at LD and 2.0 ± 0.4 ng/ml at HD. ESP was gradually elevated by 30 to 50 mm Hg from baseline using IV methoxamine and ESD continuously measured. The bradycardic effect was blocked with IV atropine. The ESP-ESD regression line was determined by the least-squares method. The slope, ESD at ESP = 100 mm Hg (ESP100) and at ESP=150 mm Hg (ESP150) were compared in control, low and high digoxin levels.

	slope±SD	r	ESP100±SD	ESP150±SD
Control	98±23	.90	3.51±.19	4.05±.26
(D) 0.9 ng/ml	100±26	.84	3.40±.16	3.93±.15
(D) 2.0 ng/ml	114±35	.90	3.45±.23	3.93±.29

The slope of the ESP-ESD relationship and the end-systolic dimension at 2 common end-systolic pressures did not change significantly at either level of serum digoxin. We conclude that the inotropic effect of chronically administered digoxin over the usual therapeutic serum digoxin range is sufficiently small as not to be demonstrable using this method.

Tuesday, March 11, 1986
10:30AM-12:00NOON, Room #366/367
Treatment of Congestive Heart Failure

ATRIAL PRESSURE AND SECRETION OF ATRIAL NATRIURETIC FACTOR INTO THE HUMAN CENTRAL CIRCULATION

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Atrial natriuretic factor (ANF), a peptide found in mammalian cardiac atria, has natriuretic and vasodilatory properties which may be important in the regulation of intravascular volume. In order to study factors related to its release in human subjects we measured pressures and plasma ANF concentrations in the central circulation of 34 patients with a variety of cardiovascular disorders. Plasma ANF concentration increased from the vena cava to the right atrium (63±20 pg/ml to 135±39 pg/ml, p=.001) and from the vena cava to the aorta 63±20 pg/ml to 148 ± 31 pg/ml, p=.001). Mean right atrial pressure was postively correlated with ANF concentration in the pulmonary artery (r=.58, p=.001), and mean pulmonary capillary wedge pressure was positively correlated with ANF concentration in the aorta (r=.64, p=.001). In a subset of patients in whom ANF concentrations were measured at two different levels of atrial pressure, increased atrial pressure was accompanied by increased ANF concentration. ANF levels measured in fresh myocardium from a patient undergoing cardiac transplantation showed tissue concentrations in the atria 500-fold higher than tissue concentrations in the ventricles. These data document that ANF is found in human atrial myocardium and suggest that ANF is released in response to increased atrial pressure. Such a secretory release mechanism is consistent with the hypothesis that ANF plays a role in the regulation of circulatory volume.

VERY HIGH CONCENTRATIONS OF IMMUNOREACTIVE ATRIAL NATRIURETIC FACTOR (IR-ANF) IN THE HUMAN CORONARY SINUS

Raoul Bonan, M.D., F.A.C.C., Simon Kouz, M.D., Gilbert Gosselin, M.D., Martial G. Bourassa, M.D., F.A.C.C., Jolanta Gutkowska, Ph.D., Jacques Genest, M.D., and Marc Cantin, M.D., Ph.D., Montreal Heart Institute and Clinical Research Institute of Montreal, Quebec, Canada

Blood samples were collected for plasma IR-ANF determinations at different cardiovascular sites during routine cardiac catheterization in 10 patients: 5 with valvular heart disease, 2 with congenital heart disease, 2 with coronary artery disease and 1 with atypical chest pain and normal coronary anatomy. A recently developed direct radio-immunoassay for human plasma was used to measure IR-ANF (Biochem. Biophys. Res. Comm. 1985; 128: 1350-1357). The plasma concentrations for these 10 patients were (mean±S.D.):

	IR-ANF pg/ml	p value
Femoral vein =	97.64± 53.90	
Right atrium =	96.51± 39.64	
Right ventricle =	128.79± 66.59	NS*
Systemic artery =	114.09± 51.20	
Coronary sinus =	451.48±282.70	<0.005†

* Two by two comparisons for all 4 values; † compared with all 4 other sites.

The systemic arterial concentration of IR-ANF in 7 normal subjects during cardiac catheterization was 94±37 pg/ml. We conclude: 1, Higher IR-ANF concentrations in our patients could be related to the stress of cardiac catheterization and to premedication (diazepam, 10 mg p.o.); 2, However, the fact that IR-ANF concentrations were 2 to 6 times higher in the coronary sinus than in all other sites remains unexplained. Although a contribution from the ventricles cannot be ruled out, this difference is probably due to release of the factor from the atria into the existing atrial veins and into the coronary sinus.

COMPARATIVE EFFECTS OF TWO CONVERTING-ENZYME INHIBITORS ON RENAL FUNCTION IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE: A PROSPECTIVE RANDOMIZED CLINICAL TRIAL.

Milton Packer MD, FACC, Wai Hung Lee MD, Norma Medina RN, Madeline Yushak RN. Mount Sinai School of Medicine, New York, NY

By causing efferent postglomerular arteriolar vasoconstriction angiotensin II (AII) preserves glomerular filtration in patients (pts) in heart failure (CHF); hence, suppression of AII synthesis by converting-enzyme inhibition (CEI) is frequently accompanied by worsening azotemia. To determine if short-acting and long-acting CEIs differ in their effects on renal function, we randomized 42 pts with CHF to either captopril (CPT, 50 mg TID, n=21) or enalapril (ENL, 20 mg BID, n=21) for 1-3 months, during which time diuretics were unaltered and no K supplements were given. Mean arterial pressure (MAP, mm Hg), weight (wt, kg), plasma renin activity (PRA, ng/ml/hr), serum creatinine (SCr, mg/dl) & serum potassium concentrations (K, meq/l) and creatinine clearance (CCr, ml/min) were measured before (pre) and after CEI. * = p<.05 (pre vs drug); † = p<.05 (CPT vs ENL)

	MAP	Wt	PRA	SCr	CCr	K
Pre	84.4	66.4	3.6	1.4	49.2	4.3
CPT	67.2*	65.1*	34.5*	1.5	55.2	4.3
Pre	81.0	65.7	8.4	1.3	54.0	4.1
ENL	66.7*	66.2	14.7*†	1.7*	44.1*†	4.6*†

Despite similar peak ↓ in MAP, ENL (but not CPT) produced ↑ in SCr and ↓ CCr, possibly because its hypotensive effects were more prolonged. Persistent ↓ in MAP and CCr likely limited the natriuretic and enhanced the antikaliuretic actions of ENL; hence, wt did not ↓, and K ↑. In contrast, CPT ↓ wt (thereby eliciting a greater reactive ↑ in PRA) and did not ↑ K.

In conclusion, ENL is more likely than CPT to cause renal insufficiency in CHF pts, probably because of its more prolonged hypotensive effects and its more prolonged antagonism of the beneficial postglomerular actions of AII. Hence, short-acting CEIs may be safer than long-acting CEIs in CHF pts.

DISCREPANCY BETWEEN FIRST DOSE ACE INHIBITION AT REST AND SUBSEQUENT ACE INHIBITION DURING EXERCISE IN HEART FAILURE.

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At rest (R), low initial dose ACE inhibition (ACEI) appears to completely block converting enzyme in heart failure (CHF), without additional blockade during chronic ACEI at higher doses. In NYHA Class 2-3(n=8) or 4(n=1) patients, we studied first dose ACEI at supine R for 7h after low dose captopril (12.5 mg) or lisinopril (5 mg), as well as 4-8 wks later at higher doses (captopril 25-50 mg, lisinopril 10-15 mg). Plasma renin activity (PRA) and plasma aldosterone (aldo) were also assessed during upright treadmill exercise (E) after 4 wks at each dose. E duration increased 16% with low dose and 22% with higher dose ACEI. At R, initial low dose and later higher doses produced almost identical reductions in plasma aldo and blood pressure, indicating similar ACEI. PRA changes were also insignificantly different between low and higher doses at R. However, during later E at the same work load as before ACEI, low dose and higher doses produced differing levels of ACEI. Low doses caused insignificant elevations of PRA compared to pre ACEI peak E (13.7±4 vs 7.4±2 ng/ml/h, p>.16) and insignificant reductions of plasma aldo (308±43 vs 381±94 pg/ml, p>.48). However, at the same E level higher dose ACEI increased PRA (to 20.4±1.3 ng/ml/h, p<.01) and plasma aldo was lower (190±28 pg/ml, p<.08) than pre ACEI. Thus, first dose ACEI at rest may not reflect later ACEI during E. High doses may be necessary to produce full ACEI during E in CHF. The more complete ACE blockade may be a factor in improved E tolerance during higher dose chronic ACEI.

HEMODYNAMIC EFFECTS OF SELECTIVE DOPAMINE-1 RECEPTOR STIMULATION: COMPARISON OF INTRAVENOUS FENOLDOPAM AND NITROPRUSSIDE IN HEART FAILURE PATIENTS.

Carlos A. Leon, M.D., A. Addison Taylor, M.D., Connie Kingry, R.N., James Norton, M.S., Craig M. Pratt, M.D., F.A.C.C., Robert Roberts, M.D., F.A.C.C., James B. Young, M.D., F.A.C.C., Baylor College of Medicine, Houston TX.

Dopamine-1 receptors (DA_1R) mediate hemodynamic effects (HE) which may be beneficial in pts with congestive heart failure(CHF). There is at present a paucity of data on DA_1R stimulation in pts with CHF. Using intravenous fenoldopam(FEN) (a selective DA_1R agonist), we evaluated in a crossover, randomly assigned study the HE of FEN and compared them to nitroprusside(NP) in 13 pts with CHF NYHA III-IV (range EF 11-30%). Infusion of both drugs was given until optimal HE were obtained. This same dose was then continued for a 6 hr period. Below are HE at baseline(B), 1 hr, and 2 hr, for NP and FEN (*p<.01 compared to B): (Mean±SEM)

	FEN-B	FEN-1h	FEN-2h	NP-B	NP-1h	NP-2h
HR	98±5	99±3	102±3	92±5	89±4	89±5
MBP	88±3	73±2*	76±2*	88±3	70±2*	70±2*
MPAP	41±3	38±3	37±4	41±3	31±2*	31±3*
PCW	26±3	26±3	25±3	27±3	19±2*	19±2*
RAP	16±2	17±2	16±2	15±2	11±1*	11±1*
CI	1.8±.2	2.9±.3*	3.0±.4*	1.9±.1	3.0±.3*	3.0±.3*
SVR	1778±147	959±102*	1006±127*	1725±123	915±83*	904±99*
PVR	393±59	203±29*	190±27*	358±53	191±27*	200±41*
SVI	20±3	30±4*	32±4*	21±3	33±3*	34±3*

We have demonstrated, for the first time, that selective DA_1R stimulation with IV FEN causes a significant reduction in SVR and BP with concomitant increase in CI and SVI which is not associated with preload diminution. The effects persisted during the 6-h period and there was no significant difference in the magnitude of systemic vasodilation between FEN and NP.

ACUTE HEMODYNAMIC RESPONSES TO ORAL FENOLDOPAM, A DOPAMINE RECEPTOR AGONIST, IN CHRONIC CONGESTIVE HEART FAILURE.
Bruce C. Wilson, M.D., Gary S. Francis, M.D., F.A.C.C., Susan M. Ziesche, R.N., and Janet A. Nelson, R.N., VAMC and University of Minnesota, Minneapolis, Minnesota.

Fenoldopam mesylate is a selective dopamine (DA_1) receptor agonist which has been demonstrated to enhance renal blood flow and sodium excretion. In order to evaluate the acute hemodynamic effects of this drug in chronic congestive heart failure (CHF), we studied 8 male patients (pts) between the ages of 54 and 69 (mean, 61.9 years) with class II or III chronic CHF. Following an oral dose of 100 mg fenoldopam, hemodynamic and regional blood flow measurements were made over 4 hours. Cardiac index increased from 2.25±0.18 (±S.E.M.) to 2.83±0.22 L/min/m^2 ($p<.01$) and systemic vascular resistance decreased from 1496±74 to 1083±383 dynes sec cm^{-5} ($p<.01$). There was a trend for mean arterial pressure to decrease (90±2 to 80±3 mmHg, p=.06) and for left ventricular filling pressure to decrease (25±5 to 21±4 mmHg, p=.06). Heart rate was statistically unchanged. Renal blood flow index was decreased acutely (34 to 30 units, $p<.05$) and after 4 days of treatment (33 to 24, $p<.05$). There were no changes in hepatic or forearm blood flow indexes acutely or after 4 days of treatment. Sodium excretion was unchanged. In conclusion, oral fenoldopam acutely improves cardiac index in pts with CHF, but this improvement is not accompanied by acute enhancement of regional blood flow or sodium excretion.

NONSUSTAINED VENTRICULAR TACHYCARDIA: UTILITY OF ELECTROPHYSIOLOGIC STUDY TO GUIDE THERAPY
Alfred E. Buxton, M.D., FACC, Francis E. Marchlinski, M.D., FACC, John U. Doherty, M.D., Mark E. Josephson, M.D., FACC University of Pennsylvania, Philadelphia, PA

We performed programmed stimulation in 56 consecutive patients (pts) with coronary artery disease and nonsustained ventricular tachycardia (VT-NS). Sustained (S) VT was induced in 24 pts who had a mean ejection fraction of 38%, vs 46% in pts without inducible VT-S (p=NS). In Group I (42 pts) therapy was guided by results of programmed stimulation: pts were given antiarrhythmic therapy only if VT-S was induced, or if spontaneous VT-NS caused symptoms: 22 pts received pharmacologic therapy, and 20 were not treated. In Group II (14 pts) treatment was not based on programmed stimulation: 11 received empiric therapy, and 3 no therapy. VT-S was induced in 17 Group I pts vs 8 Group II pts (p=NS). The ejection fraction in Group I was 42% vs 39% in Group II (p=NS). After a mean follow-up of 28 months, 8 pts died suddenly. Sudden death occurred in 6 of 24 pts with inducible VT-S vs 2 of 32 pts without inducible VT-S (p=.055). Sudden death occurred in 2 Group I pts vs 6 Group II pts (p=.002). Sudden death occurred in 0/20 untreated and 2/22 treated Group I pts, vs 2/3 untreated and 4/11 treated Group II pts (p=.002). The ejection fraction of pts with sudden death was 37% vs 43% in pts without sudden death (p=NS). We conclude that among pts with spontaneous VT-NS and coronary artery disease: 1) antiarrhythmic therapy guided by programmed stimulation is superior to empiric antiarrhythmic therapy in prevention of sudden death, 2) pts who do not have inducible VT-S have a low probability of sudden death and do not require antiarrhythmic therapy if the VT-NS is asymptomatic.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #364/365
Ventricular Arrhythmias: Electrophysiologic Testing I

ELECTROPHYSIOLOGIC STUDIES IN PATIENTS WITH NONSUSTAINED VENTRICULAR TACHYCARDIA AND CORONARY DISEASE: RELATION OF VENTRICULAR ANEURYSM TO INDUCIBLE TACHYCARDIA AND PROGNOSIS. Richard C. Klein, M.D., F.A.C.C., Charles Machell, M.D., VA Medical Center, Albuquerque, N.M.

To assess the role of electrophysiologic studies (EPS) in patients (pt) with nonsustained ventricular tachycardia (NSVT) and coronary artery disease (CAD) 22 pt with NSVT (5 beats) on Holter monitoring and cath-documented CAD underwent EPS. Prior myocardial infarction was present in 14 pt and discrete left ventricular aneurysm (LVAn) was present in 11 pt. EPS included single, double and triple premature stimulation at 3 drivecycles and 2 ventricular sites. Sustained VT (15 seconds) was induced in 9/11 pt with LVAn and 2/11 without LVAn (p 0.01). All VT were uniform in morphology; VT cycle length was 301±96 msec. EPS defined effective (no inducible VT) therapy in 3/9 pt with LVAn and 1/2 pt without LVAn. During followup (2-32 months) 5/11 with inducible VT and 1/11 without inducible VT had sustained VT or sudden cardiac death (p 0.05). 4/5 pt with EPS-induced VT and VT during followup had LVAn. 1 pt without inducible VT but VT during followup also had LVAn. Subsequent VT/VF was not related to characteristics of induced VT. Of the 5 pt with EPS-induced VT and VT during followup, effective therapy could not be defined by EPS testing in 4. In pt with CAD and NSVT the presence of LVAn defines a subgroup with a high incidence of inducible VT at EPS. This group of pt is at high risk for sustained VT or sudden death and require aggressive antiarrhythmic therapy.

OUTCOME IN NON-SUSTAINED VENTRICULAR TACHYCARDIA: RELATION TO CLINICAL FACTORS, SPONTANEOUS AND INDUCED VENTRICULAR ARRHYTHMIAS. William P. Batsford, M.D., Linette Sudbrink, R.N., Stephen I. Stark, M.D., Craig A. McPherson, M.D., Eleanor E. Kennedy, M.D., Lynda E. Rosenfeld, M.D. Yale University, New Haven, CT.

To identify potential prognostic factors we analyzed clinical features, characteristics of spontaneous arrhythmias and results of electrophysiology studies (EPS) in 81 patients with nonsustained ventricular tachycardia (VT). Coronary artery disease(CAD) was present in 26 pts, congestive cardiomyopathy(CM) in 25 pts, miscellaneous diagnosis(MISC) in 14 pts and no known structural heart disease(NKSHD) in 16 pts. Average followup was 17 months(range 1-52).

At EPS sustained VT was induced in 17/81(21%); nonsustained VT in 36/81(45%); 28/81(34%) were nonducible(< 5 nonstimulated ventricular beats with ventricular pacing and 3 programmed extrastimuli). Sudden cardiac death or recurrent symptomatic VT occurred in 9/53 pts with inducible VT and 0/28 pts without inducible VT($p < .02$). Prognosis was the same in pts with inducible nonsustained VT or sustained VT(5/36 vs 4/17, p=NS).

Clinical features (disease state, neurological symptoms, LVEF) and characteristics of spontaneous VT (cycle length, duration, morphology, and regularity) were not significant prognostic factors. No pts with NKSHD died although 1 had recurrent symptomatic VT.

Therefore: 1)Clinical features and characteristics of spontaneous VT do not identify high risk patients. 2)The presence of inducible nonsustained VT or sustained VT at EPS identified those pts likely to have sudden cardiac death or recurrent VT. 3)EPS is a useful prognostic test in pts with clinical nonsustained VT.

PROSPECTIVE COMPARISION OF RIGHT AND LEFT VENTRICULAR STIMULATION IN THE INDUCTION OF VENTRICULAR TACHYCARDIA.
Huang-Ta Lin, MD, David E Mann, MD, FACC, Jerry C Luck, MD, FACC, Sharon A Magro, PAC, Valerie Sakun, PAC, Christopher R C Wyndham, MD, FACC. Baylor College of Medicine, Houston, TX.
To assess the relative efficacy of right (RV) and left ventricular (LV) stimulation to induce (ind) ventricular tachycardia (VT), we used a tandem protocol rotating thru 3 sites (RV apex, RV septum, LV apex) with 1-4 extrastimuli (ES) at drive cycle length 500 msec and burst pacing. Spontaneous (spont) arrhythmia in the 38 patients (pts) was sustained monomorphic VT (SMVT) in 32 (29 recorded in 12-lead ECG), and sudden death in 6 pts. SMVT was induced in 28 pts from:

	RV only	LV only	Both RV+LV	Total Ind	Not Ind
All induced SMVT	5	1	22	28	10
VT similar to spont VT	5	3	9	17	12

For each ES and burst, cumulative yield of all SMVT from LV stimulation was less than that from RV, as follows:

	N	1 ES	2 ES	3 ES	4 ES	Burst
RV	38	8	17	24	26	27
LV	38	5	13	19	22	23

Induction of VT similar to spont VT followed the same trend. Of pts with VT induced from both LV and RV, the number of ES needed was:

	greater in LV	LV=RV	RV>LV
All induced SMVT	8	14	0
VT similar to spont VT	3	6	0

Analysis of RV apex data alone still showed superior efficacy over LV stimulation for induction of SMVT, and comparable efficacy for VT similar to spont VT.
Conclusion: In this prospective study, failure to induce SMVT in the RV would have necessitated LV stimulation in only 1 of 28 pts. For each ES, the yield from RV is greater than from LV. Induction of SMVT from the RV usually requires fewer or the same number of extrastimuli.

EFFECT OF EXERCISE ON THE INDUCTION OF VENTRICULAR ARRHYTHMIAS BY PROGRAMMED VENTRICULAR STIMULATION
Gregory S Thomas, M.D.,M.P.H., Michael JE Davis, M.B.,B.S., Gregory D. Curfman, M.D., G William Dec, M.D., Charles A Boucher, M.D., F.A.C.C., William R Slater, M.D., Brian McGovern, M.B., Hasan Garan, M.D., Jeremy N Ruskin, M.D., F.A.C.C., Massachusetts General Hospital, Boston MA.
To assess whether the result of programmed ventricular stimulation (PVS) is affected by exercise, PVS was performed before, during, and immediately following exercise in a select group of 8 patients (pts). All pts had previous myocardial infarction; 4 had stable angina. Seven of the 8 pts had spontaneous ventricular tachycardia (VT), 1 had ventricular fibrillation. Seven pts were taking an antiarrhythmic drug at the time of the study. At the RV apex, 1 - 2 extrastimuli were introduced during ventricular pacing at rest, during supine symptom-limited bicycle exercise, and during the first 5 minutes of recovery from exercise. The maximum workload was 31 ± 22 watts (mean ± SD). Exercise-induced ischemia was documented at this workload in 6 pts by the occurrence of either angina or a thallium-201 perfusion defect with redistribution. The result of PVS during exercise and recovery was the same as at rest in 6 pts (in 2, sustained VT was induced under all conditions, while, in 4, sustained VT could not be induced under any conditions). However, in 2 pts sustained VT was not induced at rest but was induced during exercise (1 pt) or during recovery (1 pt). Both of these pts had exercise-induced ischemia. These preliminary data demonstrate that PVS during exercise is feasible and indicate that PVS may produce different results at rest, during exercise or during recovery.

SPONTANEOUS VENTRICULAR ARRHYTHMIA ON AMBULATORY ELECTROCARDIOGRAPHIC RECORDINGS FAIL TO PREDICT WHICH PATIENTS HAVE INDUCIBLE VENTRICULAR TACHYCARDIA DURING ELECTROPHYSIOLOGIC TESTING.
Craig M Pratt, MD, FACC, Beth Thornton, RN, Sharon Magro PAC, Robert Roberts, MD, FACC, Christopher R C Wyndham, MD, FACC, Baylor College of Medicine, Houston, TX.
A recent trial claimed that inducible(I) ventricular tachycardia(VT) during electrophysiologic testing(EPS) can be predicted by using ambulatory electrocardiographic recordings(AECG). To investigate this possibility, we selected 80 patients (pts) age 58±13 (65♂,15♀) admitted for: spontaneous sustained(S) VT (N=54), cardiac arrest (n=4), ventricular fibrillation (n=11), syncope(n=11). EPS produced ISVT in 53 pts (defined as VT>120/minute for >30 seconds +/or requiring intervention); 27 pts did not have ISVT during EPS despite utilizing an identical EPS protocol with up to 4 extrastimuli and two right ventricular (RV) stimulation sites(RV apex and RV septum). AECG recordings were performed off antiarrhythmic therapy an average of 2.5 days from the baseline EPS study. For the 53 pts with ISVT, AECG (mean-22 hrs) showed 248±52 premature ventricular complexes (PVC)/hour(hr), 1.2±.3 couplets (C)/hr, and 15±6 runs VT/day, as compared to 164±51 PVC/hr, 1.0±.4C/hr and 3±1.3 runs VT, respectively in the 27 pts without ISVT by EPS(all p=ns). PVC distribution on AECG in the groups with and without ISVT on EPS:

EPS	0-9 PVC/hr	10-29 PVC/hr	>30 PVC/hr
ISVT(n=53)	25%	15%	60%
NO ISVT(n=27)	41%	11%	48%

Of the 27 pts without ISVT 21 had <1 C/hr on AECG vs 36/53 pts with ISVT(p=ns). There was no VT on AECG in 29/53 pts with ISVT during EPS as compared to 18/27 pts without ISVT (p=ns). Conclusion: No single or combined AECG criteria of arrhythmia complexity predicts pts who would have ISVT during electrophysiologic study.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #364/365
Defibrillation

VALUE OF FIELD EXPERIENCE IN IMPROVING AUTOMATIC EXTERNAL DEFIBRILLATORS.
W. Douglas Weaver, MD, FACC, Deborah Hill, BA, Carol Fahrenbruch, MSPH, Michael Copass, MD, Alfred Hallstrom, PhD, Carl Morgan, MSEE, Leonard A. Cobb, MD, FACC. University of Washington, Seattle, WA.

An automatic external defibrillator was used by first responding fire fighters prior to arrival of paramedics to initially treat 359 patients discovered in cardiac arrest. The device(D1) was recently modified(D2) in an attempt to improve the rhythm detector for the last 61 (17%) patients. One hundred fifteen (81%) of 142 patients discovered in ventricular fibrillation(VF) were shocked one or more times; 92 (77%) of 119 were shocked with D1 vs 23 (100%) of 23 using the D2, p <.001. D1 correctly identified low amplitude VF of <200uV in 11 (17%) of 64 analyses and coarse VF in 139 (63%) of 221 analyses. D2 more often correctly identified both fine and coarse VF; 9 (90%) of 10 and 32 (86%) of 37 correct analyses respectively; p <.001 and p=.003. No inappropriate shocks were delivered with either D1 or D2. Twenty-six (22%) of patients shocked had regained spontaneous circulation before paramedic arrival; 76 (53%) of 142 VF patients were admitted to hospital and 38 (27%) were discharged alive. D2 was able to deliver the first shock sooner (1.4 vs 1.9 min, p<.01) and delivered more shocks per patient (1.7 vs 1.3, p<.05) than did D1.

We conclude that automatic external defibrillators can be used by minimally trained first responding emergency rescuers and permit early resuscitation of a portion of patients prior to arrival of paramedics. Extensive field experience with such devices is mandatory in order to optimize the detector and further shorten the delays until defibrillation.

EFFICACY AND SAFETY OF TRANSVENOUS CARDIOVERSION OF RAPID VENTRICULAR TACHYCARDIA USING TWO ENERGY WAVEFORMS: A PROSPECTIVE RANDOMIZED STUDY.

Stephen T Rothbart,MD,FACC, Sanjeev Saksena,MD,FACC, Demetris Pantopoulos,ME,Ricardo Calvo,MD. Newark Beth Israel Med Ctr, Newark, NJ.

Transvenous cardioversion(TC)has limited efficacy in very rapid ventricular tachycardia(VT)&frequently results inVT acceleration(A).We examined the efficacy&safety of 2 different energy waveform tilts in9pts with rapid VT & organic heart disease.Using a Medtronic6880catheter positioned at theRV apex,VT episodes(E)with cycle lengths(CL) <360ms induced during electrophysiologic(EP)studies were treated with an incremental shock protocol of 1.0,2.5,5.0, &10.0J using 2 waveform tilts(27%&82%)at each energy level in a random fashion.

RESULTS:	27% TILT	82% TILT	p(27%vs82%)
Total #shocks:	22	23	>.2
Mean shock energy(J):	2.0	2.3	>.2
#VTE attempted:	16	15	>.2
#VTE cardioverted:	4	6	>.2
Mean cardioversion energy(J):	1.4	3	>.2
VT acceleration:	2	2	>.2

The meanVTCL for successful termination was295ms at27% tilt&275ms at82%tilt(p>.2).SuccessfulVT termination was only achieved inVTCL>210ms.Using either waveform,10of17 (59%)VTE withCL>210were terminated.

CONCLUSIONS:1)RapidVT can be successfully terminated in selected cases withTC;2)VT<CL 210preclude the use of this technique;3)Comparable efficacy rates are obtained with 27%&82%tilt waveforms in very rapidVT;4)VT acceleration duringTC with both waveforms requires availability of transthoracic cardioversion whenever this technique is employed.

MECHANISM OF EFFICACY OF TRANSVENOUS CARDIOVERSION OF VENTRICULAR TACHYARRHYTHMIAS AS DETERMINED BY CARDIAC MAPPING IN MAN.

Sanjeev Saksena,MD,FACC,Stephen T Rothbart,MD,FACC,Ricardo Calvo,MD,Demetris Pantopoulos,ME, Syed M Hussain,MD,FACC. Newark Beth Israel Med Ctr, Newark, NJ

Transvenous cardioversion(TC)is effective in terminating ventricular tachycardia(VT)&fibrillation(VF),but the electrophysiologic(EP)mechanisms in man have not been directly studied.We analyzed theEP effects ofTC shocks(0.03-25J)in 10pts with CAD & VT/VF during preoperative&intraoperative cardiac mapping using a multi-electrode plaque array with simultaneousRV&LV electrogram recordings.Synchronous(SYN) &asynchronous(AS)TC shocks were delivered at the RV apex using a Medtronic 6880 lead in sinus rhythm, VT & VF.

RESULTS:AS TC shocks of 0.03J in sinus rhythm produced immediate local RV depolarization&subsequently conducted to distant RV & LV sites after 30to80ms.Shocks of 0.05to0.5J produced immediate depolarization of larger RV&LV regions with shocks >0.5J producing immediate depolarization of distantLV sites.SYN successfulTC shocks duringVT produced either:1)immediateVT termination due to conduction block; or2)repetitiveV responses(RVR)beforeVT termination.ImmediateVT termination occurred despite prior depolarization of site of VT origin(SO).RVR's due toTC shocks showed alteration in 1)VT rate at theSO&2)the pattern ofRV&LV activation.AS high energy(>10J)termination ofVF showed instantaneous depolarization of both RV & LV.

CONCLUSIONS:1)TC shocks produce conduction block in human ventricle & its extent is dependent on shock energy;2)VT termination with TC shocks at very low energies is due to either direct conduction block in an adjoiningSO or indirectly by a paced depolarization penetrating a distant SO; 3)HigherTC energies(>0.5J)alter conduction at a distantSO directly resulting in VT instability or termination & in RV & LV.

POST-DEFIBRILLATION BRADYCARDIA FOLLOWING IMPLANTABLE DEFIBRILLATOR DISCHARGE.

Edward V. Platia, MD, FACC, Enrico P. Veltri, MD, Lawrence S.C. Griffith, MD, FACC, Philip R. Reid, MD, FACC, Thomas Guarnieri, MD, FACC, Levi Watkins, Jr., MD, Morton M. Mower, MD, FACC, M. Mirowski, MD, FACC, The Johns Hopkins Medical Institutions and Sinai Hospital, Baltimore, MD; and Washington Hospital Center, Washington, DC.

We examined the incidence and nature of post-defibrillation bradycardias immediately following automatic implantable cardioverter-defibrillator (AICD) discharge. Our patient (pt) population consisted of 111 pts, whose mean age was 58 yr (range 19-77 yr). Sustained ventricular tachyarrhythmias were induced post-implant to test the AICD. Six pts had previously had a permanent VVI pacemaker implanted.

The AICD discharged 17.2 $\pm$ 6.1sec (mean $\pm$ SD) after the initiation of the induced tachyarrhythmia. At time of AICD discharge (mean energy 27 $\pm$ 3.2 joule) VT was present in 37 pts and VF in 74 pts. Following AICD discharge the first spontaneous beat occurred after 1.4 $\pm$ .7sec: the rhythm was sinus in 38, junctional in 68 pts, and atrial fibrillation in 5 pts. In 2 pts the temporary pacemaker was turned on after asystole lasted over 4 sec, and a permanent VVI pacemaker subsequently implanted. The duration of the post-discharge pause was the same for VT (1.2sec) and VF (1.5sec) (p=NS). In pts with implanted pacemakers, pacing initiated the post-discharge rhythm. During followup (21 $\pm$ 9 mo) there was no clinical evidence of prolonged post-discharge asystole in those pts with documented AICD discharges.

We conclude that significant post-discharge asystole is rare in pts with AICDs. Nonetheless, the integrity of the escape mechanism should be assessed in each pt prior to hospital discharge.

SUBTHRESHOLD INTRACARDIAC CARDIOVERSION SHORTENS VENTRICULAR TACHYCARDIA CYCLE LENGTH AND IS A PREDICTOR OF CARDIOVERSION THRESHOLD.

Rahul Mehra, PhD, Eric N. Prystowsky, MD, FACC, William M. Miles, MD, James J. Heger, MD, FACC, Scott R. Spielman, MD, FACC, Douglas P. Zipes, MD, FACC. Krannert Institute of Cardiology, Indianapolis, IN.

We analyzed the cycle length (CL) of the first beat (FB) following synchronized subthreshold Cardioversion (C) in 37 patients with 47 morphologically distinct ventricular tachycardias (VTCL:407 $\pm$ 87 msec) to determine the relationship between the duration of reset (VTCL minus FBCL) and the amplitude of the C stimulus as well as the ability of the reset to predict C threshold. C shocks up to 5 joules (< 450 volts) were delivered through the Medtronic 6880 endocardial lead. Among the 172 unsuccessful C episodes, the FBCL was shorter than VTC in 116 (67%); equal to VTCL in 53 (31%) and longer than VTCL in 3 (2%). In 43 VTs where multiple unsuccessful C attempts were made, there was a positive correlation between the duration of the reset and the C voltage ($r = .37$; $p<.01$) and between the reset and delivered energy ($r=.21$; $p<.05$). In 26 VTs where the threshold of successful C was >.15 joules, the maximum reset measured at <.15 joules was found to be a significant predictor of whether the threshold of C would be less than 1 joule. (Logistic Regression Analysis, p=.012). The greater the reset at <.15 joules, the higher was the probability that the C threshold was less than 1 joule. Conclusions: 1) C shocks that do not terminate VT frequently shorten the FBCL. 2) The duration of the reset increases with increasing voltage or energy output of the C. 3) Greater reset measured at low energy subthreshold shocks predicts a greater likelihood that the C threshold will be less than 1 joule. These findings are consistant with reentry as the mechanism of VT and may be used to screen responders for successful Cardioversion.

SEQUENTIAL PULSE DEFIBRILLATION USING A CATHETER AND SKIN ELECTRODE

Michael J. Kallok, PhD, Douglas L. Jones, PhD, George J. Klein, MD, FACC, Medtronic, Inc., Minneapolis, MN

Sequential pulse defibrillation (SPD), in which a pulse is delivered from the SVC to RV apex (RVA), followed 1 msec later by a second pulse delivered from a left heart (LH) electrode to RVA, has been shown to reduce defibrillation threshold (DFT) by 50% or more compared to single pulse catheter defibrillation. We have previously described the use of an epicardial patch, coronary sinus catheter, and subcutaneous plate (SUBCU) as the LH electrode with similar DFT's obtained with each system. The objective of this study was to compare DFT obtained with a SUBCU electrode to those obtained with each of three skin electrodes (48 cm^2, 109 cm^2, 172 cm^2 surface area, respectively). Seven halothane anesthetized dogs had a defibrillation catheter (Medtronic 6880) introduced into the right ventricle and a SUBCU electrode (33 cm^2) implanted over the left 4th intercostal space. DFT was determined by SPD shocks delivered after electrical induction of VF. The SUBCU electrode was removed and DFT was then measured using each of the 3 skin electrodes. DFT's for the SUBCU and 3 skin electrodes were 10.2 $\pm$ 4.7, 10.0 $\pm$ 4.5, 11.2 $\pm$ 3.7, 9.7 $\pm$ 3.4 joules (mean $\pm$ SD), respectively. Analysis of variance indicated no significant difference in DFT among the four LH electrodes tested ($p > .10$). We conclude that low energy sequential pulse defibrillation can be accomplished with an intracardiac catheter and skin electrode. This may provide a means for preimplant testing of an implantable defibrillator that utilizes SPD, and may provide a low energy alternative to transthoracic defibrillation.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #157
Clinical Studies in Pediatric Cardiology

LIFE-THREATENING DIGOXIN TOXICITY IN CHILDREN: TREATMENT WITH DIGOXIN SPECIFIC FAB FRAGMENTS.

Thomas Wenger MD, Vincent Butler MD, Edgar Haber MD, FACC, Thomas Smith MD, FACC, Burroughs Wellcome Co., RTP, NC

Twenty pediatric cases of life-threatening digoxin toxicity have been treated with digoxin specific antibody fragments (Fab). The age range was 1 day to 4 years. Nine children became toxic from accidental ingestion. These patients ingested amounts ranging from 2.25 to 11 mg of digoxin (n=8), had serum concentrations from 6.2 to >100 ng/ml (n=9) and required Fab doses of 28 to 1,000 mg (n=9). Eleven patients developed severe toxicity during therapy for underlying heart disease. Their calculated body stores of digoxin ranged from 48 to 833 µg of digoxin (n=10); serum concentrations ranged from 5.2 to 18 ng/ml (n=9) and Fab doses ranged from 5 to 160 mg (n=11). Three cases were due to medication errors.

Nineteen of 20 children responded favorably to Fab. Reversal of toxicity was rapid, with improvement often seen within 10 min of Fab administration. Three patients required resuscitation lasting more than 1 hour for arrhythmias not responsive to any other therapy, but which reversed with Fab therapy. Nine patients had renal insufficiency (serum creatinine range 1.3 to 3.1 mg/dl). Fab requirements were the same as those with normal renal function and there was no recurrence of toxicity later.

No adverse reactions to Fab were identified other than hypokalemia, presumably caused by reversing inhibition of the Na^+,K^+ pump.

Our experience suggests that pediatric ingestions of greater than 4 mg of digoxin are likely to be life-threatening, that medication errors constitute an important cause of life-threatening digoxin intoxications, and that treatment with Fab fragments is effective and appears to be rapid and safe.

RELATIONSHIP OF THE STILL'S MURMUR, SMALL AORTIC DIAMETER AND HIGH AORTIC VELOCITY

Stanley J. Goldberg, MD, FACC, Marcy L. Schwartz, Hugh D. Allen, MD, FACC, Gerald R. Marx, MD, FACC, Neil Wilson, MD, University of Arizona, Tucson, AZ

The etiology of the innocent Still's murmur (SM) remains obscure. To evaluate possible etiologies, we studied 70 normal subjects; 29 had SM and 41 were random controls who had no murmur (-MUR). Pulsed Doppler and 2D echo were used to determine the magnitude of ascending (A) and descending (D) aortic (AO) and main pulmonary artery velocities, maximal spectral widths of all velocity tracings, AAO diameter, and the percent of each group with tricuspid regurgitation and left ventricular bands. Although SM was concentrated in the first decade of life, it was also found in the second. The most important finding by discriminant analysis was that AAO diameter relative to body surface area was significantly smaller for the SM group (21.9 mm) than for the -MUR group (28.6 mm) ($p < .001$) when other factors were controlled. As a consequence of smaller AO diameter, and since indexed cardiac output was equal in the 2 groups, mean peak AAO and DAO velocities were significantly higher in the SM group (118 cm/s and 133 cm/s, respectively) than in the -MUR group (AAO=107 and DAO=104 cm/s) ($p < .001$ and $p < .01$ respectively). No velocity gradients were found to suggest stenosis in either group. No significant differences ($p > .05$) were found when comparing SM and -MUR groups with respect to mean peak pulmonary artery velocity, AAO and DAO and pulmonary spectral widths (markers of turbulence). The presence of tricuspid regurgitation and ventricular bands was equal in both groups. The important and previously unreported findings of this study were demonstration in SM subjects of 1) significantly smaller aortas, 2) higher aortic velocities, and 3) equal cardiac outputs as compared to controls.

CHROMOSOME ABERRATIONS SECONDARY TO DIAGNOSTIC CARDIAC CATHETERIZATION

Anthony A. Raviele, M.D.; David A. Shafer, Ph.D.; Lorie A. Click, R.N., M.N.; Virginia G. Dunbar, B.S.; Cardiology Section, Pediatrics Department, Emory University School of Medicine, Atlanta, Georgia

Twenty-eight (28) patients, aged 1 day to 11.1 years (mean=4.1 yr) were studied for chromosome changes induced by diagnostic cardiac catheterization (cath). There were fourteen (14) boys and fourteen (14) girls. Eleven (11) were cyanotic and seventeen (17) were acyanotic. A sequence of four (1-ml) samples of blood from each patient were obtained and analyzed for damage: at the beginning of the cath (1), after fluoroscopy and before cineangiography (cine) (2), after cine (3), and the following morning (4). After 2-3 days in culture, double-blind chromosome analysis was performed on the average of 100 metaphases for each of the four samples. The chromosome abnormalities seen were acentrics, dicentrics, and rings. Radiation dose was calculated for each segment of the procedure. A nonparametric statistical analysis of the dose of radiation received and the amount of change seen was performed. The mean rate of occurrence of aberrations increased with the sequence number ($p=0.001$). The greatest change was noted after cine as compared to before ($p=0.001$). The number of previous caths, patients' clinical condition, and other demographic factors were not found to correlate with the frequency of aberrations. It is concluded that chromosome abnormalities are observed in pediatric patients exposed to diagnostic radiation. The long-term implications of this finding remain unknown.

CAN CARDIAC OUTPUT AND EXERCISE FACTOR BE MEASURED BY DOPPLER ECHOCARDIOGRAPHY DURING SUPINE BICYCLE ERGOMETRY?
Gerald R. Marx, MD, FACC, Richard W. Hicks, MS, Scott M. Kinzer, MS, Hugh D. Allen, MD, FACC, Stanley J. Goldberg, MD, FACC, Jack Wilmore, Ph.D., University of Arizona, Tucson, AZ

To determine if cardiac output (CO) could be measured by Doppler echo (DE) during exercise, we measured CO at rest and during supine bicycle ergometry in 19 boys, mean age 13±0.6 years. Ten subjects underwent two separate testing periods 3 months apart, and 9 were tested once, for a total of 29 studies. Pulsed Doppler velocities and aortic diameter measurements for calculation of CO were obtained at rest from the suprasternal notch with an imaging off-axis transducer. Velocities were then measured with a nonimaging, 90° off-axis 2.25 MHz transducer during exercise. Oxygen consumption was measured at rest and exercise which allowed for calculation of exercise factor (EF), the change in CO divided by the change in oxygen consumption. Mean nonindexed CO (L/min) increased from 5.6±1.0 (mean±SD) to 9.3±1.5 L/min at a predetermined 50% maximal exercise level. Simultaneously measured oxygen consumption (ml/min) increased from mean 210±40 to 895±211. The relationship of CO and oxygen consumption had a correlation of r=.92. Mean exercise factor for the group was 5.4±1.4, similar to previously invasively measured values.

We conclude that Doppler echocardiography measures cardiac output during supine exercise. When combined with simultaneously measured oxygen consumption, exercise factor can be computed. This new noninvasive methodology should have significant clinical and research potential.

LEFT VENTRICULAR WALL STRESS AND CONTRACTILE FUNCTION AFTER RASTELLI REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES.
Thomas P Graham Jr MD FACC, Rodney C G Franklin MRCP, Richard K H Wyse PhD, Vanda Gooch BSc, John E Deanfield MRCP.
The Hospital for Sick Children, Great Ormond Street, London, United Kingdom.
Abnormal RV function following intraatrial repair of transposition of the great arteries (TGA) is an established finding. However, LV function after Rastelli repair of TGA, where the left ventricle is the systemic pumping chamber, has not been evaluated. LV wall stress and contractile function were determined by echocardiography in 11 patients studied 0.7 to 13.8 yrs (mean 5.6) following Rastelli repair of TGA with ventricular septal defect and left ventricular outflow tract obstruction. Age at operation ranged from 4.6 to 11.3 yrs (mean 7.4). Data were compared with 24 normals of similar age and heart rate. LV end-diastolic dimension and volume were significantly increased above normal, averaging 134 ± 8% of normal dimension ($p<0.004$) and 104 ± 13 cc/M^2 ($p<0.007$) respectively. In addition LV wall mass was 215 ± 40 g/M^2 versus a normal value of 72 ± 6 g/M^2 ($p<0.004$). Meridional and circumferential end-systolic and peak systolic stress values were not significantly different between normal and Rastelli patients. Estimates of LV systolic function including shortening fraction, rate-corrected circumferential fiber shortening velocity (VCFc) and ejection fraction were significantly depressed when compared to normal values. VCFc evaluated as a function of end-systolic stress demonstrated abnormal contractile function in 8/11 (73%) of patients. Thus LV function is abnormal in patients following Rastelli repair of complex TGA and LV dilatation and wall hypertrophy persist.

CORONARY ARTERY ABNORMALITIES IN PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM
J. Kasznica, P. Ursell, W. Gersony, W. Blanc.
Columbia University, New York, NY

Abnormalities of the coronary circulation have been reported in cases of pulmonary atresia with intact ventricular septum (PA-IVS), however the origin of this problem has been only speculative. In PA-IVS, intramyocardial sinusoids (IS) in the right ventricle (RV), which may persist from fetal life, have been noted to communicate with the coronary circulation. To evaluate the significance of IS in PA-IVS, we studied 17 autopsy heart specimens (2 fetuses, 13 neonates, 2 infants) with PA-IVS and: a) analyzed the distribution and gross and microscopic pathology of the coronary arteries, b) inspected the RV wall for macroscopic (severely dilated) IS and c) measured RV volumes. The RV volume of 9 complete hearts was measured by silicone cast and volume displacement and compared with age- and body weight-matched normal controls. In comparison with these 9, the remaining 8 hearts were visually graded as to RV size. The 17 cases included 13 with small RV (volume <50% of control) and 4 with normal RV size. None of the hearts with normal size RV showed either IS or coronary artery abnormalities. Four of 13 with small RV (including one fetus of 23 weeks) had both IS and coronary abnormalities; each of the 4 showed absent coronary os/atrophic coronary artery (fibrous cord). One of 13 with small RV had tortuous and sclerotic coronaries but no IS. We conclude: 1) 38% of PA-IVS with small RV have major abnormalities of the coronary arteries, 2) severely dilated IS are present in 80% of PA-IVS cases with coronary abnormalities, 3) coronary abnormalities may be present in fetuses with PA-IVS as early as 23 weeks of gestation.

Tuesday, March 11, 1986
8:30AM-10:00AM, Room #267
Circulatory Regulation

ALPHA-ATRIAL NATRIURETIC FACTOR IN CARDIOVASCULAR DISEASE.
R.M. Arendt, M.D., A.L. Gerbes, M.D., D. Ritter, M.A., E. Stangl, Ph.D., P. Bach, M.D., J. Zähringer, M.D.
University of Munich, Munich, West Germany.

Recently isolated atrial peptides possess natriuretic and vascular smooth muscle relaxant properties. They are secreted upon volume and/or pressure loading. Thus, they may play a role in the modulation of cardiovascular function. We recently demonstrated the occurrence of alpha-ANF, the 28 amino acid residue portion of pre-pro-ANF in human plasma. The present investigation characterized ANF in the circulation of patients with cardiovascular disease. Plasma from normotensive controls and patients with arterial hypertension or congestive heart failure, respectively, was extracted by adsorption to resin columns. ANF plasma levels were measured in lyophilised column eluates by a sensitive and specific RIA. ANF plasma levels in patients with congestive heart failure or arterial hypertension were considerably higher than those in normotensive controls: 277 ± 125 or 62.2 ± 19.7, respectively, versus 8.7 ± 1.0 fmol/ml. ANF-immunoreactivity in plasma extracts of normotensive controls consisted exclusively of the authentic 28 amino acid peptide, whereas plasma extracts of hypertensive patients yielded an additional higher molecular weight form on high performance gel permeation chromatogrphy. Conclusions: (1) A specific RIA in conjunction with a novel extraction procedure allows for the rapid and reliable determination of ANF plasma levels. (2) Hypertensive patients or patients with congestive heart failure display a, respectively, 7- or 32-fold increase in ANF plasma levels as compared to control subjects. (3) In addition to the authentic alpha-ANF, a 13000 dalton precursor is present in the plasma of hypertensive patients.

PLASMA ATRIAL NATRIURETIC FACTOR (ANF) IS ELEVATED IN PATIENTS WITH HEART FAILURE:

Jorge Cheirif M.D., Claus Bossaller M.D., Addison A. Taylor M.D., Carolyn Williams B.S., Robert Roberts M.D., F.A.C.C. and Philip D. Henry M.D., F.A.C.C. Baylor College of Medicine, Houston, TX.

Since atrial myocardium of animals with heart failure may be depleted of ANF and exogenous ANF evokes a diuresis in animals with cardiogenic edema, we postulated that patients with heart failure and edema may be deficient in ANF. Fourteen normotensive patients with myocardial disease and edema (CHF; ejection fraction <0.35) and 9 age-matched controls (C) were studied. ANF was measured by radioimmunoassay (Peninsula) in peripheral venous blood collected in the recumbent and standing positions at 8:00 a.m. and 5:00 p.m.:

	recumbent a.m.	standing a.m.	recumbent p.m.
CHF(n=14)	644±41*	605±47	624±43
C (n=9)	353±28	326±42	332±15
p-value	<.0001	<.0005	<0.0001

*values are means ±SE in pg/ml

Reverse-phase HPLC fractionation of plasma from CHF and C patients showed a single dominant immunoreactive peak that corresponded to the peak of exogenous human α ANF. Thus, ANF varies little with respect to posture and time, and heart failure with edema is associated with a substantial elevation in circulating ANF, an appropriate response to volume expansion.

CARDIOVASCULAR EFFECTS OF BICARBONATE IN PATIENTS WITH HYPOXIA AND CARDIAC DECOMPENSATION.

Robert Bersin, M.D., Kanu Chatterjee, M.D., F.A.C.C. and Allen I. Arieff, M.D., V.A.Med. Ctr. & Univ. of California, San Francisco, Ca

Sodium bicarbonate has been used in the therapy of cardiac arrest for over 50 yrs. The assumption is that its administration will correct acidosis and thereby improve cardiac performance. However, the actual cardiovascular effects of NaHCO3 in hypoxic patients have not been well evaluated. In previous studies from our laboratory in hypoxic dogs (Science 227:754-56, 1985), NaHCO3 infusion resulted in decrements of cardiac output (CO) and mean arterial pressure (MAP) with decrements in peripheral oxygen utilization. We therefore elected to study the cardiovascular effects of NaHCO3 infusion in patients with hypoxia (pa.02=62 mmHg) and congestive heart failure (NY Heart Assoc. Class III or IV) who had ejection fraction<40%. Patients participating in this study were undergoing elective right heart catheterization and placement of a coronary sinus catheter for other reasons. To control for Na and volume status, patients received either NaHCO3 or NaCl, 2.5 mEq/kg/hr and measurements made at 15 min intervals for 1 hr of infusion and 1 hr of recovery. Measurements were made in blood of pH, pCO2, 02 content, bicarbonate & lactate, and of MAP, CO, heart rate, filling pressures & coronary sinus flow (CSF), and utilization & extraction of both oxygen & lactate by the myocardium. In the initial 30 min of infusion, there were no significant changes in CO, MAP, CSF or myocardial oxygen use. However, myocardial lactate extraction was 50% less with NaHCO3 than with NaCl (p<.01). During the last 30 min of infusion, the CO, CSF and myocardial extraction of oxygen & lactate were significantly less by 12-50% with NaHCO3 than with NaCl (p<.01).

These data suggest that in hypoxic patients with cardiac decompensation receiving NaHCO3: a) bicarbonate decreases myocardial oxygen utilization, cardiac output and coronary sinus flow, resulting in decreased ability to extract lactate; b) there appears to be increased anaerobic metabolism in the heart as a result of bicarbonate; c) the routine use of bicarbonate in such patients may require re-evaluation

HEMODYNAMIC RECOVERY DURING VENTRICULAR TACHYCARDIA: ROLE OF α AND β ADRENERGIC RECEPTOR ACTIVATION

Ted Feldman M.D., Kenneth R Gray M.D., John D Carroll M.D. The University of Chicago, Chicago Illinois

VT is hemodynamically tolerated differently by individual patients, possibly due to variations in autonomic nervous system adjustment. In 13 chloralose anesthetized dogs, VT was simulated by RV pacing (cycle length=250ms). LV function was assessed during sinus rhythm and 20 sec after initiation of VT before and after α-blockade with terazocin (n=7; 0.3mg/kg) and β-blockade with propranolol (n=6; 2mg/kg). Micromanometers measured peak LVP, minimum diastolic LVP (Pmin) and max +dP/dt. LV end-diastolic dimension (EDD) was measured with endocardial piezo crystals. Sinus interval, an index of autonomic tone, was determined immediately after termination of VT.

	CONTROL		β-BLOCKADE		α-BLOCKADE	
	NSR	VT 20s	NSR	VT	NSR	VT
LVP (mmHg)	114	94	120	78*	97	68*
Pmin (mmHg)	3.9	4.2	6.6	10.2*	2.9	3.4
+dP/dt(mmHg/s)	2108	2344	1502	1233*	2154	2194
EDD (mm)	37.7	36.2	39.3	38.6	36.0	35.7
Sinus int(msec)	511	333*	456	419	485	360*

*=p<0.05 vs sinus rhythm

Under control conditions, immediately after onset of VT there was severe hypotension. By 20 sec after onset of VT LVP recovered to sinus values and +dP/dt exceeded sinus values, despite decreased EDD and LV asynchrony. After β-blockade LVP recovery during VT was blunted, Pmin rose, and max +dP/dt failed to recover. With α-blockade VT produced a sustained fall in LVP, yet cardiac sympathetic stimulation preserved Pmin, +dP/dt recovered, and sinus rate accelerated post VT.

CONCLUSIONS: Hemodynamic recovery during VT requires both α vasoconstriction and β augmented contraction/relaxation. These functional responses may be clinically relevant since adrenergic down-regulation and agents with α or β-blocking effects are common in patients susceptible to VT and sudden death.

THE EFFECTS OF HEART TRANSPLANTATION ON MAXIMAL FOREARM BLOOD FLOW.

Lawrence I. Sinoway, M.D., John R. Minotti, M.D., Dwight Davis, M.D., John L. Pennock, M.D., F.A.C.C., Timothy I. Musch, Ph.D., and Robert Zelis, M.D., F.A.C.C. Cardiology, PA State University, Hershey, PA

The effects of heart transplantation on maximal forearm blood flow in patients (n=6) with decompensated congestive heart failure (CHF) was studied to define the relationship between the central and peripheral components in this disease. Forearm blood flow (FBF) (ml/min·100ml) was measured with a strain-gauge plethysmograph (venous occlusion technique). In addition to basal FBF, the blood flow response after release of 5 minutes of arterial occlusion, the peak reactive hyperemic blood flow (RHBF) response, was measured as an index of maximal vasodilator capacity. Minimal resistance (R) and maximal conductance (C) were derived from the RHBF and mean BP. Each subject was studied pretransplant, prior to hospital discharge (average 16 days post-transplant) and again as an outpatient (average of 63 days). We noted the following results:

	Basal FBF	RHBF	R	C
Pretransplant	1.2	21.0	4.9	.26
Predischarge	1.5	22.0	4.5	.22
Outpatient	2.2*	39.1*†	2.9*†	.42*†

*p<.05 vs pretransplant; †p<.05 vs predischarge

These results indicate that: (1) Despite a dramatic, virtually immediate, enhancement of cardiac function, peripheral indices of vasculature function remain impaired for an extended time post-transplantation. This suggests that the peripheral component is a distinct separable entity of the congestive state, (2) Delayed substantial increases in peripheral flow occur after discharge. Whether this delay represents a reduction in immunosuppressive medication, an improvement in local metabolic function, or a training effect remains to be elucidated.

NOREPINEPHRINE KINETICS IN PATIENTS WITH CONGESTIVE HEART FAILURE.

Dwight Davis, M.D., Janet Robison, John Minotti, M.D., Francis Day, M.D., Lawrence I. Sinoway, M.D., Timothy I. Musch, Ph.D., and Robert Zelis, M.D., F.A.C.C., Cardiology, PA State University, Hershey, Pennsylvania

Excessive sympathetic nervous system (SNS) activity plays an important role in both adaptive and pathophysiological mechanisms of congestive heart failure. Most investigators have relied on plasma norepinephrine (NE) levels to assess SNS activity. The steady state plasma level of norepinephrine, however, is the result of two processes, spillover (Spl) of norepinephrine into the plasma after release from sympathetic nerve terminals, and clearance (Cl) of norepinephrine from the circulation. We evaluated supine norepinephrine levels and norepinephrine kinetics in 8 normal volunteers and 4 patients with CHF utilizing a 90 minute [^{3}H]-l-norepinephrine infusion to achieve a steady state plateau concentration. Norepinephrine clearance was calculated from the infusion rate and ^{3}H-NE concentration (alumina extraction) at steady rate and norepinephrine spillover was determined from the infusion rate and norepinephrine plasma concentration (radioenzymatic technique).

	NE (pg/ml)	Cl (l/min/m^2)	Spl (n mol/min/m^2)
NL	214.8	1.435	1.954
CHF	794.6*	1.007*	4.851*

(*p<.05)

In patients with CHF, clearance was decreased by 29% and spillover was increased by 248% compared to normal subjects. Thus, previously reported elevations in norepinephrine levels of patients with CHF is due to altered kinetics involving both an increase in spillover and a decrease in clearance.

ABNORMAL RIGHT HEART HEMODYNAMICS AT REST AND DURING SUPINE EXERCISE: A COMMON FINDING FOLLOWING ORTHOTOPIC CARDIAC TRANSPLANTATION

Peter W. Pflugfelder, MD, F.Neil McKenzie, MD, William J. Kostuk ,MD, FACC, University Hospital, London, Ontario, Canada.

In order to characterize right heart hemodynamics, 21 orthotopic cardiac transplant (TP) recipients have been studied 0.5-51 mo (mean 16.1 mo) after surgery. Following routine endomyocardial biopsy, right heart pressures and thermodilution cardiac outputs were obtained with a flow directed catheter at rest (supine) and during symptom limited graded supine exercise. In addition, the effect of slow deep inspiration on right atrial (RA) pressures and wave forms was determined at rest, with passive leg raising (volume loading), and following exercise.

During exercise, striking elevations of right atrial (RA), pulmonary artery (PA) and pulmonary wedge (PW) pressures were seen:

	CO (l/min)	mean RAP (mmHg)	mean PWP (mmHg)	mean PAP (mmHg)	PVR (dyne-cm-s^{-5})
Rest	5.8±.4	6.1±0.5	13.3±0.9	21.4±1.2	112±11
Peak	11.8±0.4*	16.9±1.1*	27.6±1.3*	38.1±1.9*	73±11◊
Post	8.3±0.4*	8.0±0.8*	17.5±1.2*	29.0±2.0*	127±14

means given ±SEM; *p<.001 vs rest, ◊p<.01 vs rest

During exercise mean RAP doubled in 20 patients. Similarly, mean PWP doubled in 11 patients. A highly significant rise in mean PAP was seen despite a reduction in calculated pulmonary vascular resistance.

An abnormal (Kussmaul) inspiratory response of the mean right atrial pressure was seen in 6 patients at rest, in 11 with passive leg raising and in 12 following exercise. In these individuals, a characteristic prominent "V" wave with a markedly exaggerated "y" descent was observed with inspiration. In 6 patients with a normal RA wave form during inspiration while supine with legs down, an abnormal response developed with volume loading. In contrast, the right ventricular (RV) diastolic pressure decreased on inspiration in all patients when measured post exercise. Although an abnormal inspiratory pressure response was most common in studies less than 1 yr post TP, up to 50% of patients studied beyond 1 yr were also abnormal.

Although the cause of these common abnormal observations post TP is unknown, pericardial constraint, possibly localized to the atria is suggested.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #267
Clinical Evaluation of Complex Problems

RELATIVE VALUE OF BEDSIDE MANEUVERS IN THE EVALUATION OF PATIENTS WITH SYSTOLIC MURMURS.

Nicholas J. Lembo, MD, Louis J. Dell'Italia, MD, FACC, Michael H. Crawford, MD, FACC and Robert A. O'Rourke, MD, FACC, Univ of Tx Health Sci Ctr, San Antonio, Tx.

The relative value of bedside maneuvers in the differential diagnosis of systolic murmurs has not been systematically assessed by non-biased auscultators. Thus, we evaluated inspiration, Valsalva maneuver, rapid standing from the squatting position, handgrip exercise, and amyl nitrite inhalation in 45 patients with murmurs due to documented: aortic stenosis (AS,n=10), hypertrophic cardiomyopathy (HCM,7), mitral regurgitation (MR,15), ventricular septal defect (VSD,5), and right-sided murmurs (RSM,8). Increases (↑) or decreases (↓) in murmur intensity were evaluated by two cardiologists in adjacent areas using electronic stethophones, so that the patient and the maneuvers were unknown. The percent (%) of systolic murmurs that changed as expected were:

MANEUVER	RSM	AS	HCM	MR	VSD
Inspiration	↑100%	↓ 75%	↓ 80%	↓67%	↓70%
Valsalva	↓ 71%	↑100%	↑ 60%	↑93%	↑90%
Standing	↓ 28%	↓ 70%	↑100%	↑40%	↑50%
Handgrip	↑ 12%	↓ 30%	↑100%	↑67%	↑70%
Amyl Nitrite	↑ 50%	↑ 56%	↑100%	↑77%	↑90%

Conclusions: It is clear that inspiration best separates right-sided from left-sided murmurs. The response to Valsalva and standing usually correctly identifies the murmur of hypertrophic cardiomyopathy. The murmurs of mitral regurgitation and ventricular septal defect have parallel responses to all maneuvers but can be differentiated from the murmur of aortic stenosis by opposite responses to handgrip and amyl nitrite. Thus, the origin of most systolic murmurs can most accurately be determined when the auscultatory responses to systematically applied bedside maneuvers are analyzed in combination.

KINETICS OF LEUKOCYTE DEPOSITION DURING CANINE CARDIAC TRANSPLANT REJECTION STUDIED WITH INDIUM-111-LEUKOCYTE SCANNING.

Marvin A. Konstam, M.D., F.A.C.C., Karen Ramberg, M.S., Raymond Connolly, Ph.D., Douglas D. Payne, M.D., Boaz Avitall, M.D., Jeffrey M. Isner, M.D., F.A.C.C., David S. Weiland, M.D., Barbara A. Brockway, Deeb N. Salem, M.D., F.A.C.C., Tufts-New England Medical Center, Boston, MA

At present, direct histologic examination is the only reliable means for detecting cardiac transplant (Tx) rejection in humans or in animal models. Using gamma camera imaging of indium (In)-111-oxine-labeled leukocytes, we studied the in-vivo kinetics of leukocyte deposition in comparison with histologic evidence of rejection (0 to 3+; Billingham criteria) in 4 dogs receiving heterotopic Tx without immunosupression. Leukocyte deposition was quantified as percent of injected activity and as the ratio of Tx to native (N) heart activity(Tx/N). Beginning 4 days post Tx a progressive increase in leukocyte deposition was observed. Percent injected In (mean±SE):

	Native	Tx	Tx/N	
4 days post Tx:	1.1±0.4	1.0±0.2	1.0±0.2	p<0.05
7 days post Tx:	0.8±0.4	1.9±0.9	2.3±0.1	

In all dogs, Tx/N was ≤1.25 on day 4 but >2 by day 7. A 30% increase above initial Tx leukocyte activity corresponded to the presence of 2+ rejection based on histologic criteria.

Conclusions: Beginning 4 days following canine cardiac Tx (without immunosupression) progressive leukocyte deposition occurs as detected by In-leukocyte scanning and correlates with histologic rejection. In-leukocyte scanning is a valuable tool for studying kinetics of leukocyte deposition and Tx rejection in animal models and, potentially, in man.

NONINVASIVE CHARACTERIZATION OF THE PATHOLOGIC CHANGES IN PRIMARY PULMONARY HYPERTENSION. Stuart Rich MD, FACC, Giuseppe G. Pietra MD, Kim Hart RN, Karen Kieras RN, Bruce H. Brundage MD, FACC. University of Illinois, Chicago IL.

Primary pulmonary hypertension(PPH) has been attributed to 3 different pathologic etiologies: plexogenic arteriopathy(PLEXO), microthromboemboli(THROMBO), and veno-occlusive disease(VENO). We evaluated the chest x-ray(CXR) and pattern of peripheral blood distribution on perfusion lung scan in 30 pts who fulfilled the NIH registry criteria for PPH and categorized the lung fields on CXR as normal (28) or increased bronchovascular markings (2) and the blood flow on lung scan as normal (19) or diffuse non-segmental patchy abnormalities (11). These were correlated with pathologic specimens from 11 pts obtained from open lung biopsy(4) or autopsy(7) which were graded based on the vascular changes and presence of microthrombi with the pathologist blinded from the results of the CXR and lung scan. The findings were:

	CXR		LUNG SCAN	
	normal	inc. markings	normal	patchy
PLEXO	5	0	5	0
THROMBO	4	0	1	3
VENO	0	2	0	2

Each group was significantly different from the other ($p<0.05$, Fishers exact test). We conclude that by characterizing the vascular markings on CXR and pattern of perfusion lung scans in pts with PPH one may be able to differentiate those with PLEXO, THROMBO, or VENO changes on pathology. The patchy defects noted on the lung scan in some pts appears to reflect vascular occlusion. Based on these data, PLEXO is the most common histologic type (63%), with THROMBO intermediate (30%) and VENO the least common (7%) in our experience. These findings may have important implications regarding the selection of vasodilators or anticoagulants as therapy for pts with PPH.

THE EFFECT OF HIGH DOSE CYCLOPHOSPHAMIDE AND TOTAL BODY IRRADIATION ON LEFT VENTRICULAR FUNCTION IN ADULT LEUKEMIC PATIENTS UNDERGOING ALLOGENEIC BONE MARROW TRANSPLANTATION Ernesto B. Baello, M.D., David W. Ferguson, M.D., Mark D. Ensberg, M.D., John W. Kugler, M.D., Roger D. Gingrich, M.D., Ph.D., James O. Armitage, M.D., Lynell W. Klassen, M.D., Richard E. Kerber, M.D., F.A.C.C., Melvin L. Marcus, M.D., F.A.C.C., Peter T. Kirchner, M.D., David J. Skorton, M.D., F.A.C.C. University of Iowa, Iowa City, IA

Protocols used to prepare leukemic patients for bone marrow transplantation have the potential for cardiac toxicity due to the administration of high-dose cyclophosphamide and total body irradiation. We have reported one regimen, combining cytarabine, cyclophosphamide (90 mg/kg) and total body irradiation (900 rads), which is relatively effective in the treatment of leukemia. To assess cardiac effects of this protocol, we performed serial echocardiography and radionuclide ventriculography in 17 leukemic patients (ages 18-45, mean 31, 12 males) undergoing allogeneic bone marrow transplantation. RESULTS: One and six days after cyclophosphamide, no significant change in echocardiographic left ventricular fractional shortening or increase in left ventricular diastolic dimension was seen. At an average of 77 days (range 28-358) after transplant, radionuclide ventriculography revealed no significant change in resting ejection fraction in the group as a whole (58 ± 6.8% [SD] vs. 56 ± 8.0%, p=NS). In four patients, resting ejection fraction fell into the abnormal range (from mean ejection fraction of 56% to 44%, lowest = 41%). Ten patients also had exercise radionuclide ventriculography and all had normal responses (>5% increase with exercise) pre- and post-transplant.

We conclude that this effective bone marrow transplantation regimen has little short-term cardiac toxicity in the majority of patients.

DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF CARPENTIER MITRAL VALVULOPLASTY John Kenny, MD, Lawrence Cohn, MD, FACC, Richard Shemin, MD, FACC, John J. Collins, MD, FACC, Maureen Plappert, Martin St. John Sutton, MD, FACC, Cardiovascular Division, Brigham & Women's Hospital, Boston, MA.

Doppler echocardiographic (DE) studies were performed in 16 patients (10 males) aged 33 to 77 (mean 58) to evaluate the results of Carpentier Ring mitral valvuloplasty (CV). At pre-op cardiac catheterization 15 patients had severe mitral regurgitation (MR) and 1 had mitral stenosis and regurgitation. Mitral valve disease was due to myxomatous degeneration in 7 pts, ischemic heart disease in 5, rheumatic heart disease in 2, dilated cardiomyopathy in 1 and calcified mitral valve annulus in 1. Early post-operative DE studies were performed with the sample volume in the left atrium to map out regurgitant flow, and in the left ventricle to record mitral diastolic flow. MR was classified as Grade I if the MR jet extended only into the first ¼ of the left atrium, Grade II if the jet extended into the second ¼, Grade III if the jet extended into the third ¼ and Grade IV if it was detected throughout the left atrium. We assessed LV inflow obstruction as pressure half time, mitral valve area and mitral valve gradient derived from Doppler mitral diastolic flow. Following CV 9 patients had no MR, 5 had Grade I MR and 2 had Grade II MR. Peak diastolic mitral valve gradient was 7.5 ± 3.0 mmHg, mean diastolic gradient was 3.0 ± 1.2 mmHg and pressure half-time was 83±22 msec giving a calculated mitral valve orifice area of 2.9 ± 0.9 cm^2. We conclude 1) that CV reduces MR without obstructing LV inflow. 2) DE is an excellent method of evaluating the results of CV. 3) DE is of value in the longitudinal follow-up of individual patients.

Tuesday, March 11, 1986
8:30AM–10:00AM, Room #268
Factors Influencing Myocardial Metabolic Function

EXERCISE TRAINING INFLUENCES CARDIAC ISOMYOSIN COMPOSITION IN NORMAL AND DIABETIC RODENTS. Gregory Curfman, M.D., John Fallon, M.D., Pamela Tupper, B.A., William Skornik, M.S., Glen Spaulding, D.V.M., Ban-An Khaw, Ph.D., Edgar Haber, M.D. Massachusetts General Hospital, Boston, MA.

Although endurance-exercise training (ET) influences cardiac contractile state, the molecular mechanisms involved are not well understood. We therefore studied the effect of ET on cardiac isomyosin (CIM) composition in 24 normal rats, 24 diabetic rats (streptozotocin 60 mg/kg), and 12 normal hamsters. Half of each group underwent ET by forced swimming for 2 months (rats), or by voluntary running for 1 or 2 years (hamsters), while the other half were sedentary (SED). V3 CIM was quantified in LV and RV extracts using anti-V3 monoclonal antibody as a probe in conjunction with an ELISA procedure.

The results are summarized in tabular form:

	%V3(LV)		%V3(RV)	
	SED	ET	SED	ET
Normal Rats	26+/-7	11+/-7*	29+/-13	20+/-7*
Diabetic Rats	82+/-15#	47+/-26*	87+/-10	42+/-9*
Hamsters (1 yr)	67+/-7	39+/-4*	49+/-2	20+/-2*
Hamsters (2 yr)	95+/-6	81+/-4*	60+/-4	41+/-3*

(*p<0.001 vs. SED; #p<0.001 vs. normal SED)

The data show that both forced and voluntary ET significantly reduced the V3 CIM content of the LV and RV in normal rodents. This effect was attenuated in 2 yr-old hamsters, because spontaneous running declined with advancing age. We confirmed that diabetes results in a large increase in V3 CIM content. However, the diabetes-induced CIM switch was prevented and reversed by ET, partly owing to improved glucose intolerance in trained diabetic rats (mean fasting glucose: SED 554 mg%, ET 320 mg%, p<0.01).

Exercise-induced switches in CIM composition in normal and diabetic rodents represent a molecular adaptation of the contractile apparatus to the exercise-trained state.

EFFECTS OF DIABETES ON CARDIAC CONTRACTILE PROTEINS IN THE RABBIT.

Pia S. Pollack, M.D., Ashwani Malhotra, Ph.D., Fred S. Fein, M.D., F.A.C.C., James Scheuer, M.D., F.A.C.C. Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York

In diabetic (D) rats, cardiac myosin ATPase activity decreases and a shift from the previous dominant V_1 isoenzyme to V_3 occurs, correlating with depressed contractility. Rabbit myocardium is mostly V_3, but small isoenzyme shifts might be responsible for some of the cardiac contractile abnormalities in the D rabbit. Male rabbits were made diabetic with 140-150 mg/kg of alloxan. Myosin ATPase activity (μ mole Pi/mg/min) and isoenzyme distribution in controls (C) and D were (N=6-8):

	3 Day		1 Month		3 Month		6 Month	
	C	D	C	D	C	D	C	D
Ca^{2+}-activated myosin ATPase	.36	.40	.36	.28+	.43	.33+	.46	.28+
$\%V_3$ isoenzyme	82	75	80	93+	77	90+	73	95+

When 3-4 month D rabbits received insulin for 3-4 months, the results were:

	C	D	Treated D
Ca^{2+}-activated myosin ATPase	.48	.34+°	.45
Actin activated myosin ATPase	.126	.105+	.116
$\%V_3$ isoenzyme	78	95+°	79

(+p<.05 vs C; °p<.05 vs treated D).

These results correlate with mechanical changes in papillary muscle from these same hearts. In rabbit, as in rat, changes in cardiac contractility correlate with changes in myosin isoenzyme composition and are reversible with insulin.

EFFECT OF ATP PRECURSOR ADMINISTRATION ON POST-ISCHEMIC FUNCTION AND METABOLISM IN ISOLATED RABBIT HEARTS.

Giuseppe Ambrosio, M.D., William E. Jacobus, Ph.D. and Lewis C. Becker, M.D., F.A.C.C., Johns Hopkins Medical Institutions, Baltimore, MD.

Loss of purine nucleotides during early reflow is considered to be a causative factor for the prolonged depression of myocardial ATP content and cardiac function seen after reversible ischemic injury in "stunned" hearts. Supplementation with ATP precursors would therefore seem to be a logical approach to accelerate functional and metabolic recovery of post-ischemic hearts. In this study we employed a model of ischemia and reperfusion in the isolated rabbit heart in which myocardial levels of ATP were continuously monitored by 31-Phosphorus-NMR spectroscopy. Isovolumic developed pressure (DP) was also simultaneously assessed by means of a balloon inserted into the left ventricle. After equilibration, the hearts were subjected to 20 min of total global ischemia at room temperature and reperfused for 2 hrs with perfusate containing either adenosine (ADO) 100 μM (n=6), or 5-aminoimidazole-4-carboxamide riboside (AICAR) 100 μM (n=6), a direct precursor of purine nucleotides; 6 additional hearts received normal perfusate (controls). Ten min NMR spectra were acquired during baseline and throughout ischemia and reperfusion. During reperfusion DP reached 80-85% of baseline in control hearts; myocardial ATP levels, which were reduced to 74.6+4.4% of baseline by the end of ischemia, did not recover, actually decreasing by an average of -12.5%/2 hr. ADO treatment did not induce any difference in function, DP being 78-82% of baseline; in all hearts, however, ATP synthesis was significantly accelerated by ADO treatment, by an average of +13.4%/2 hr ($p < 0.005$ vs controls). AICAR-treated hearts did not show any difference from controls in either function or ATP levels, possibly as a consequence of the reported inhibition of adenylosuccinate lyase, a key enzyme in the purine salvage pathway, by this drug. These data indicate that in this experimental model, administration of ADO after ischemia significantly increases myocardial levels of ATP without improving post-ischemic function. Although ATP levels and function are both depressed in the post-ischemic heart, there is an apparent dissociation between function and myocardial ATP content, and the two may therefore not be directly related.

HISTAMINE EFFECT ON CONTRACTION FREQUENCY, Na INFLUX AND CYCLIC AMP IN CULTURED HEART CELLS ARE MEDIATED THROUGH H_2 RECEPTORS.

Charles Y. Lui, M.D., and David McCall, M.D., Ph.D., F.A.C.C., Univ of TX Health Sci Ctr, San Antonio, TX.

Histamine (H) has been shown to have both positive inotropic and chronotropic effects. To evaluate the chronotropic effects, spontaneously contracting monolayers of cultured rat myocardial cells were treated with H, 10^{-7}M-10^{-4}M. This resulted in a dose-dependent increase in contraction frequency reaching a maximum in 10^{-5}M. Contraction frequency increased to (mean ±SEM) 129±3.5%, 151±7.8%, 177±2.82% and 180±3.7% of control in 10^{-7}M, 10^{-6}M, 10^{-5}M and 10^{-4}M, respectively (for each n=10, p<0.001). The effect was time-dependent taking 30 min to develop fully. Changes in contraction frequency were accompanied by parallel increases in the verapamil (V)-sensitive Na influx. V-sensitive Na influx (p-mole/cm^2/sec) increased from a control of 10.45±1.44 (mean ±SEM) to 24.34±2.41 and 32.57±2.35 at 10 and 30 min treatment with 10^{-6}M H (n=5, p<0.001). These data fit the previously described relationship between V-sensitive Na influx and contraction frequency. Cimetidine (cimet) (10^{-4}M) but not diphenhydramine (D) (10^{-4}M), abolished both the rate and Na influx response to H. Subsequent studies showed a dose- and time-dependent elevation of cAMP with H treatment. Cell cAMP (control=5.25 p-mole/mg protein) increased by 30%, 57%, 94% and 224% in 10^{-7}M, 10^{-6}M, 10^{-5}M and 10^{-4}M H respectively, the changes between 10^{-7}M and 10^{-5}M closely paralleling the changes in beating rate and Na influx. H effect on cAMP was competitively inhibited by cimet. The results suggest H increases beating rate by increasing V-sensitive Na influx and that the effects are mediated by H_2 receptors coupled to adenylate cyclase.

IMPAIRED FATTY ACID METABOLISM AS A SIGN OF MILD REGIONAL ISCHEMIA IN CANINE MYOCARDIUM.

Markus Schwaiger, M.D., Michael C. Fishbein, M.D., F.A.C.C., William Wijns, M.D., Mark Block, M.S., Herbert Hansen, B.S., Carl Selin, M.S., Michael E. Phelps, Ph.D., Heinrich R. Schelbert, M.D., F.A.C.C., UCLA School of Medicine, Los Angeles, California.

Positron emission tomography in dogs previously demonstrated abnormal C-11 palmitate kinetics in the center of ischemia but also, to a lesser degree, in myocardium with only mildy reduced blood flow. To study this finding in the same experimental model, electronmicroscopic (EM) examination was performed in 11 closed chest dogs after a 3 hr balloon occlusion of the left anterior descending artery. The affected vascular territory was defined by dye injection. Necrosis was determined by TTC and regional blood flow (MBF) by microspheres. Tissue samples for EM were taken from the center and border of the ischemic segment and from normal myocardium. In the center, MBF was 14.2 ± 16.7 ml/min/100 g with classic signs of necrosis on EM. In the border, EM revealed normal glycogen and mitochondria. The only abnormality (8 of 11 dogs) were lipid droplets adjacent to mitochondria. MBF in this area averaged 51.4 ± 18.4 ml/min/100 g, which is only 38% lower than in normal myocardium (82.5 ± 18.5 ml/min/100 g) which was free of lipid droplets. Thus, consistent with the abnormal C-11 palmitate kinetics, the deposition of lipid droplets on electron microscopy indicates impaired fatty acid metabolism while the preserved glycogen stores suggest compensatory metabolic adaptation in states of mildly reduced myocardial blood flow.

QUANTIFICATION OF MYOCARDIAL CREATINE KINASE SUBFORMS IN BIOPSIES FROM PATIENTS UNDERGOING CARDIAC TRANSPLANTATION. Carlos A. Leon, M.D., James B. Young, M.D., FACC, Peter R. Puleo, M.D., Michael D. Schneider, M.D., Mary Anne Bresser, M.S., Robert Roberts, M.D., FACC, M. Benjamin Perryman, Ph.D., Baylor College of Medicine, Houston, Tx.

Three subforms of MM creatine kinase (CK) exist in the blood, MM-3 the tissue form and MM-2 and MM-1 occurring as a result of proteolysis by plasma carboxypeptidase-N which removes the C-terminal lysine. Preliminary studies suggest detection of the newly released tissue form (MM-3) provides for earlier diagnosis of infarction. More recently, we have shown rapid release of MM-3 has potential value as a noninvasive marker to assess reperfusion during thrombolytic therapy. These studies imply a single tissue MMCK subform in the myocardium and inability of the myocardium to convert MM-3 to the other subforms which is yet to be validated in man. Protease degradation limits the validity of postmortem myocardial CK subform analysis. Thus, the present study was performed on biopsies from patients undergoing cardiac transplantation. Biopsies were analyzed for total CK and CK subforms. A total of 184 biopsies were obtained from either RV, LV, or septum which were endocardial for donor hearts (n=140) and transmural for recipients (n=44). Samples were obtained in liquid nitrogen, homogenized, and analyzed for MMCK subforms on agarose gel electrophoresis. MMCK activity ranged from 2.38-3.3 x 10^4 IU/mg of protein and the subform was consistently the tissue subform, namely MM-3, with no trace of MM-2 or MM-1. These results indicate myocardial CK is solely MM-3 and conversion to MM-2 or MM-1 occurs post-release in the blood. Thus, an increased level of MM-3 in the circulation reflects release from tissue and early rapid release in the setting of infarction is likely to reflect reperfusion.

RECEPTOR TRAFFIC IN THE MYOCARDIUM: COMPARISON OF a- AND B-ADRENERGIC RECEPTORS
Alan S. Maisel, Harvey J. Motulsky, Paul A. Insel. UCSD and VAMC, Ja Jolla, CA

We previously demonstrated that myocardial ischemia causes an externalization of beta-adrenergic receptors (BAR) from intracellular light vesicles to the surface plasma membrane. As alpha-adrenergic receptors (AAR) have been shown to increase in cardiac membrances after ischemia, we tested for AAR internalization and externalization in response to agonists and ischemia. In one group of guinea pigs we gave epinephrine (0.25 mg/kg sq) and sacrificed animals at 45 min; another group underwent left anterior descending coronary artery ligation for 1 h. We used differential centrifugation of left ventricular tissue to prepare a sarcolemmal membrane and light vesicle fraction. AAR and BAR number were quantitated by binding of [125I]ICYP and [^{3}H]prazosin, respectively.

	B-receptors membranes vesicles (fmol/mg)		a-receptors membranes vesicles (fmol/mg)	
Control	90	80	86	24
epinephrine	54	130	55	26
Ischemia	135	45	142	22.

Fewer AAR than BAR were present in light vesicles, and changes in AAR distribution in these fractions appeared not to explain agonist or ischemia-induced alterations in sarcolemmal receptors. Thus the traffic of AAR in myocardium is apparently different than that of BAR.

Tuesday, March 11, 1986
10:30AM–12:00NOON, Room #268
Receptors—Mechanisms of Action and Modulation of Function

CANINE CARDIAC β_1-ADRENERGIC RECEPTOR CHARACTERIZATION AND AGONIST-STIMULATED PHOSPHORYLATION OF THE ISOLATED β_1-ADRENERGIC RECEPTOR.
Jeong H. Im, Ph.D., Hazel R. Bowdon, B.A., Steve W. Puckett, Ph.D. and W.T. Woods, Jr., Ph.D. Departments of Pharmacology, and Physiology and Biophysics, U.A.B., Birmingham, Alabama.

To characterize β_1-adrenergic receptors, membrane proteins solubilized from canine ventricular myocytes were fractionated by chromatography on ion exchange and Sepharose CL-6B columns, successively. The fractionated samples were photoaffinity labeled with 15-(4'-azidobenzyl)-1-^{125}I-carazolol (^{125}I-ABC). Alternatively, the ion exchange fractionated samples were labeled with ^{125}I-ABC, and then chromatographed on a Sepharose CL-6B column. Three β_1-adrenergic receptor complexes with Mr of >600K, 440K and 110K were obtained. Upon SDS-PAGE, the complexes were dissociated into 66K-Da and 58K-Da subunits. To test β-agonist-stimulated phosphorylation, the purified β_1-receptor was incubated in the absence and presence of D,L-, D-, and L-isoproterenol (ISO) for 30 min, then exposed to (γ-^{32}P)-ATP. Analysis by SDS-PAGE of the incubation mixtures showed that D,L- and L-ISO stimulated the receptor phosphorylation, but D-ISO had no effect. This result suggests that agonist-stimulated β_1-receptor phosphorylation may be directly related to physiological function of β_1-receptors. Mn^{++} was required for the phosphorylation. The phosphorylation was stimulated by cAMP, inhibited by a tyrosine modifying agent tetranitromethane and by P_i, but GTP had no effect. The results of the phosphorylation experiments suggest that the agonist-stimulated β_1-receptor phosphorylation may be the initial reaction for the desensitization of the receptor.

α-1 ADRENERGIC RECEPTOR REGULATION OF ATRIOPEPTIN RELEASE FROM THE RAT HEART. Mark G. Currie, Ph.D. and Walter H. Newman, Ph.D., Dept. of Pharmacology, Medical University of South Carolina, Charleston, S.C.

Recent studies have shown that the atria are the source of a bioactive peptide, atriopeptin (AP), that may be a major regulator of the renal and cardiovascular systems. Our goal in the present study was to determine whether the release of immunoreactive AP (iAP) from the isolated perfused rat heart was influenced by adrenergic receptor stimulation. The data show that the infusion of epinephrine and norepinephrine stimulated the release of iAP into the coronary effluent. The β-agonist isoproterenol and the α-2 agonist BHT-920 lacked effects on iAP release. However, the α-1 agonist phenylephrine produced a dose-dependent release of iAP. In the presence of phentolamine this release was competitively inhibited with a 28X shift in the ED_{50} (1.2 x 10^{-6} M vs. 3.4 x 10^{-5} M).

	Basal iAP pcg/ml	Treated iAP pcg/ml	fold increase
Control	320±60	340±60	1.1
Epinephrine (1X10^{-6}M)	220±40	580±80*	2.6
Norepinephrine (1X10^{-6}M)	180±40	540±100*	3.0
Isoproterenol (1X10^{-6}M)	280±40	320±40	1.1
BHT-920 (1x10^{-6}M)	200±40	220±30	1.1
Phenylephrine (5X10^{-7}M)	280±40	420±110	1.5
Phenylephrine (5X10^{-6}M)	280±40	555±180*	2.0
Phenylephrine (5X10^{-5}M)	280±40	940±200*	3.4

Mean values ± S.E. * $p < 0.05$ vs basal

We conclude that AP release is stimulated by α-1 receptor activation. This finding suggests an involvement of the sympathetic nervous system in the physiologic regulation of AP secretion.

AMILORIDE POTENTIATES THE POSITIVE INOTROPIC EFFECT OF ACETYLSTROPHANTHIDIN IN CANINE CARDIAC PURKINJE FIBERS.
Kathleen K. Brown, D.V.M., Anne C. Marchese, M.D., Augustus Grant, M.D.,Ph.D., and Harold Strauss, M.D.
Duke University Medical Center, Durham, N.C.

The concurrent use of amiloride (A) and digitalis glycosides improves cardiac function unrelated to the K sparing effect. To evaluate the possibility that a greater rise in both intracellular sodium activity ($\alpha^i Na$) and peak isometric tension (T) are produced by acetylstrophanthidin (ACS) in the presence of A, $\alpha^i Na$, T, and action potential (AP) characteristics were measured. Potentiation of ACS inotropy was seen by measuring T in stimulated (1 Hz) fibers repeatedly exposed to .1μM ACS both before (T_1) and after (T_2) 2 hr exposure to 10μM A. In fibers treated with ACS+A, T_2/T_1 was, on average, 1.72 contrasted with 1.13 in fibers repeatedly exposed to glycoside alone. No significant change in T was produced by A alone. AP duration was increased 32%±2.1 by A. $\alpha^i Na$ measurements are summarized below: (mean±SEM, mM, n=6).

	Control	ACS	A	ACS+A
$\alpha^i Na$	8.45±1.3	10.87±1.6	7.94±0.9	10.86±1.0
$\Delta\alpha^i Na/\Delta 100\%T$		1.28±0.2		0.93±0.1

Changes in AP duration are therefore unrelated to an increase in steady-state $\alpha^i Na$ in the presence of A. Prolongation of phase 2 of the AP may result in transient increases in $\alpha^i Na$. During Na-K pump inhibition by ACS, this could augment $\alpha^i Ca$, resulting in greater inotropy.

EFFECTS OF HYPOXIA ON BETA AND ALPHA ADRENERGIC RECEPTOR DENSITY IN ISOLATED MAMMALIAN CARDIAC MYOCYTES
Ryuichi Matsuo, M.D., Junichi Hayashi, M.D., Hideharu Manabe, M.D., Yoshio Watanabe, M.D., F.A.C.C., Cardiovascular Institute, Fujita Gakuen Health University, Toyoake, Aichi, Japan.
To precisely determine the kinetics of adrenergic receptors, we studied the effects of hypoxia on beta and alpha adrenergic receptor density(ARD) in cardiac cells. Myocytes were isolated from adult rat hearts, and were incubated under standard culture conditions. The binding of high specificity, high specific activity radioligands, [125-I]-pindolol(IPIN) and [125-I]-HEAT(IHEAT), was used to quantitate beta and alpha adrenergic receptors, respectively. Equilibrium was reached with a 20-minute period of binding assay. Specific binding defined by bound IPIN (or IHEAT) displaceable by propranolol(or prazosin) averaged 86±7%(or 65±7%) at low IPIN(or IHEAT) concentrations, was saturable, reversible and stereospecific. Cardiac myocytes were divided into two groups, being cultured in 50%O_2-5%CO_2-45%N_2, and the other in 10%O_2-5%CO_2-85%N_2. After 1 hour incubation, beta ARD was increased in myocytes under 10%O_2 (1163±104 x10^3receptors(R)/cell) as compared to that under 50%O_2 (912±83 x10^3 R/cell)($p<0.05$, n=6), without significant changes in their affinity (1053±750 vs 875±470 pM). Alpha ARD under 10%O_2 (204±23 x10^3R/cell) was higher than that under 50%O_2 (162±20 x10^3R/cell) ($p<0.05$, n=6), again with no changes in their affinity. Similar results were also seen after 3 hour incubation. Conclusions: 1)ARD in living myocytes was increased in hypoxia. 2)Beta and alpha receptors had similar kinetics and did not show reciprocal changes in hypoxia. 3)IPIN and IHEAT are useful tools for investigating receptor kinetics in mammalian adult myocytes under experimental conditions such as hypoxia and/or ischemia in vitro.

ALPHA 1 AND ALPHA 2 RECEPTOR STIMULATION IN CONSCIOUS DOGS INCREASE CORONARY RESISTANCE BUT NOT MYOCARDIAL FUNCTION.
Rainald Seitelberger,M.D., Brian D. Guth,Ph.D., Jong-Dae Lee,M.D., Kazuhiro Katayama,M.D., Gerd Heusch,M.D. and John Ross,Jr.,M.D.,FACC, UC San Diego, La Jolla, California.

There is little information on the role of coronary alpha 1 and alpha 2 receptors in the conscious state, and some studies suggest that alpha 1 stimulation causes a positive inotropic effect. Accordingly, dogs were chronically instrumented with an intracoronary (IC) catheter for drug infusion and a flow probe on the circumflex coronary artery (CX). Sonomicrometers were implanted to assess regional systolic wall thickening (%WT). After beta blockade with propranolol (1mg/kg, iv.), CX end-diastolic resistance (EDCR) was used to assess the response to various alpha agonists. Alpha 1 agonists (methoxamine, M, 20μ g/kg. and phenylephrine, P, 6μ g/kg, given IC) increased EDCR an average of 23.6% ($p<0.01$, n=9). This increase was blocked by 0.04mg/kg of the selective alpha 1 blocker prazosin (+5.7%, NS, n=6). The mixed agonist norepinephrine (NE, 0.5μ g/kg) increased EDCR by 24.3% ($p<0.05$, n=9). The selective alpha 2 blocker idazoxan (0.05mg/kg) antagonized this effect almost entirely (+6.9%, NS, n=6), whereas no change was observed after prazosin (+28.2%, $p<0.05$, n=6). Without beta blockade the alpha 1 agonist M did not affect %WTH, whereas P increased %WTH (21.2 ± 4.0 vs 27.1 ± 5.4, $p<0.01$, n=6). This effect was eliminated by beta blockade. The selective alpha 2 agonist BHT 920 (6μ g/kg) had no effect on %WTH.
Therefore, in conscious dogs (1) alpha 1 and alpha 2 receptors are equipotent in increasing coronary resistance, (2) the increase in coronary resistance due to NE is mainly mediated by alpha 2 receptors, and (3) alpha 1 and alpha 2 receptors do not alter myocardial function.

Tuesday, March 11, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 9:00AM–10:00AM
Hall D, Georgia World Congress Center
Pharmacology-Antiarrhythmic Drugs—Basic

ANTI-FIBRILLATORY ACTIVITY OF ACUTE AMIODARONE ADMINISTRATION: AN EFFECT INDEPENDENT OF CLASS III ANTI-ARRHYTHMIC ACTIVITY?
Roger A. Marinchak, M.D., Kathleen M. O'Connor, M.S., Ted D. Friehling, M.D., Peter R. Kowey,. M.D., F.A.C.C., Medical College of Pennsylvania, Philadelphia, Pa.

Administered acutely, amiodarone exhibits anti-adrenergic activity which may protect against ventricular fibrillation (VF). We compared RV and LV VF thresholds with results of programmed extrastimulation (PES) before (T_1), 30-45 (T_2) and 90-100 (T_3) minutes following amiodarone, 5 mg/kg acutely, then 0.42 mg/kg/hr IV in 9 cats 2 weeks after proximal left anterior coronary artery occlusion and in 6 sham operated cats. Mean heart rate decreased significantly in both groups without significant change in arterial blood pressure after amiodarone. Mean VF thresholds rose significantly at T_2 and T_3 for the infarcted but not sham animals. Five of 9 (56%) of the infarcted cats had PES-induced VT before amiodarone. Of these, 4 (44%) and 2 (22%) had inducible VT at T_2 and T_3 (pNS). For these 5 cats, VF thresholds were (RV/LV, mean+SE, mA): T_1 (11.6 + 4.9/ 15.2+3.4); T_2 (50.6+16.6/50.4+15.6); T_3 (47.5+23.9/45.3+22.1); ($p=0.03$, T_1 vs T_2, ANOVA). No PES-induced VT occurred in sham cats. Mean effective refractory periods increased significantly after amiodarone in infarcted and sham cats without significant change in dispersion of refractoriness. Amiodarone's acute anti-fibrillatory effect is temporally discordant with prevention of VT induction and may be related to rapid onset of potent anti-adrenergic activity in addition to Class III anti-arrhythmic properties.

EFFECT OF INTRAVENOUS DESETHYLAMIODARONE IN DOGS WITH MYOCARDIAL INFARCTION AND INDUCIBLE VENTRICULAR ARRHYTHMIAS.

Hoshiar Abdollah MB, F. James Brennan MD FACC, and James F. Brien PhD. Departments of Medicine and Pharmacology, Queen's University, Kingston Canada.

To determine if desethylamiodarone (DA), the major circulatory metabolite of amiodarone, has antiarrhythmic activity, we administered DA intravenously to 4 dogs with reproducibly-inducible ventricular tachycardia or fibrillation (VT/VF) one week after the production of myocardial infarction by a 2-hour balloon occlusion of the left anterior descending artery. DA was administered as a 5 mg/kg bolus followed by a 2-hour infusion of 8 mg/kg/hr. Electrophysiologic testing was repeated at 30 min intervals during DA infusion, and plasma [DA] was measured simultaneously using an HPLC assay. [DA] in healthy and infarcted myocardium was measured at the end of the infusion. DA ameliorated the arrhythmias in all 4 dogs: in 2 VT/VF was not inducible and in the other 2 inducible VF was converted to inducible, stable, well-tolerated VT after 60-120 min of DA infusion. [DA] in plasma, healthy, and infarcted myocardium at the end of the infusion were 0.66 ± 0.34 μg/ml, 57.2 ±30.48, and 11.89 ± 5.58 μg/g, respectively. These preliminary data suggest that DA 1) has antiarrhythmic activity, 2) accumulates rapidly in the myocardium, and 3) is preferentially distributed into healthy as opposed to infarcted myocardium.

EFFECT OF INTRAVENOUS AMIODARONE ON VENTRICULAR FIBRILLATION DURING OUT-OF-HOSPITAL CARDIAC ARREST

Michael Kentsch, M.D., Klaus-Peter Kunze, M.D., Walter Bleifeld, M.D., F.A.C.C., Dept. of Cadiology, University Hospital Eppendorf, Hamburg, West Germany

In 1981-1982 35 patients (pts) with out-of-hospital cardiac arrest due to ventricular fibrillation (VF) were unresponsive to standard drug therapy and 3 or more DC countershocks. As a result of further therapy 8 of these 35 pts were successfully resuscitated with subsequent admission to hospital. Because of this low success rate we investigated the effect of intravenous (i.v.) amiodarone on VF unresponsive to repetitive DC countershocks and standard drug therapy. In 1983 - 1984 we studied pts with out-of-hospital cardiac arrest due to monitored VF. After standard resuscitation including application of i.v. sodium bicarbonate (1mg/kg bw), initial DC countershock, i.v. lidocaine at a dose of 100 mg and 2 further ineffective DC countershocks, in the study group an amiodarone bolus of 300 mg was injected and DC countershock was repeated (group A, n=10). In the control group (group B, n = 10) pts were treated with additional lidocaine (100 mg) and repetition of DC countershock. In group A a stable cardiac rhythm was established in 5 of 10 pts. Three pts, 2 with VF, 1 with asystole, required further therapy before haemodynamic stabilisation was achieved. Of 10 pts in group A, 8 were successfuly resuscitated and admitted to hospital. In group B initial control was obtained in 2 pts. After identical additional therapy 3 of 10 pts were admitted to hospital in group B ($p < .05$). Mean number of DC countershocks was 4.60 (± 1.07) in group A and 6.70 (± 2.41) in group B ($p < .05$). There were no significant differences in age, sex, response time of rescue and mobile energency care units and history of previous cardiac arrest between the 2 groups. In pts with out-of-hospital cardiac arrest due to VF, unresponsive to repeated DC countershocks and i.v. lidocaine, i.v. amiodarone appears to be an effective antiarrhythmic agent.

ORAL LOADING WITH AMIODARONE INCREASES VENTRICULAR DEFIBRILLATION THRESHOLD WITH IMPLANTED ELECTRODES IN DOGS

Lawrence H. Frame, M.D., F.A.C.C., Ned Hoffman, B.A., Steve A. Kolenik, III, B.A., Jeffrey H. Sheldon, B.S., University of Pennsylvania, Philadelphia, PA

We studied the effect of oral and IV amiodarone(AMIO) on ventricular defibrillation threshold(DFT) because of reports of patients taking AMIO that are refractory to cardioversion (CV) with the Automatic Implantable Defibrillator(AID). CV was performed using an apical LV patch electrode and RA spring electrode in closed chest pentobarbitol anesthetized(30 mg/kg) dogs weighing 20-25 Kg. DFT was measured every 15 min over 3 h by giving incremental shocks (3,5,10,15,20,25,30,35 and 40 joule) starting 20 sec after the onset of ventricular fibrillation until CV was achieved. We studied the effect of oral AMIO by comparing a control group to two treatment groups that received 200 mg(9.5±0.1 mg/Kg) or 400 mg(18.4±1.3 mg/Kg) po per day for 9 days (six dogs in each group). The table shows group means (±SE) for the average DFT for each dog (1st line) and the highest DFT for each dog (2nd line).

	Control	AMIO 200 mg po qd	AMIO 400 mg po qd
Mean DFT (Joules)	8±0.8	15.6±2.2	18.0±1.3
Highest DFT (Joules)	12.5±1.2	19.1±2.2	31.7±2.3

Oral AMIO significantly raised DFT in a dose dependent manner (analysis of variance for significance and Tukey's method to compare groups, $p<.05$). In 5 other dogs the DFT during a 1 h control period (10.2±0.2J) was not different from the DFT within 2 h after giving IV AMIO(5mg/Kg) (10.8 ±0.5J).

We conclude that in normal dogs 1) oral loading with therapeutic doses of AMIO raises DFT in a dose dependent manner but 2) this effect is not seen within 2 h after IV AMIO. This lends support to the evidence for AMIO-induced resistance to cardioversion in patients with an AID.

FREQUENCY AND DIRECTION-DEPENDENT EFFECTS OF SINGLE AND COMBINATION ANTIARRHYTHMIC DRUGS ON CONDUCTION VELOCITY IN VIVO.

Harry A. Kopelman, MD, Ashok K. Bajaj, MD, John P. Wikswo, Jr., PhD, Luc M. Hondeghem, MD, PhD, Raymond L. Woosley, MD, PhD, Dan M. Roden, MD, FACC, Vanderbilt University, Nashville, TN.

Factors influencing ventricular conduction velocity (CV) include fiber orientation and the fast inward sodium current (i_{Na}). Mexiletine (M) and quinidine (Q) depress i_{Na} in a cycle length (CL)-dependent manner, with in vitro time constants for recovery (τ_r) from CL-dependent i_{Na} depression of 0.5-1 sec (M) and 4-8 sec (Q). The effects of M(1.8±0.4 μg/ml) and Q(4.5±1.7 μg/ml) and M+Q, a clinically effective drug combination (M: 2.0±0.4; Q: 4.5±1.3 μg/ml), on CV were therefore evaluated in 24 open chest dogs. The AV node was ablated to allow measurements over a wide range of CL. An electrode array consisting of a central coaxial stimulating pair and close bipolar pairs 3 and 6 mm away in multiple orientations was sewn to the left ventricular epicardium. In each experiment, CV (m/sec; $\bar{x}$±SD) was determined from interbipole conduction times in both a rapidly and slowly propagating orientation and compared to baseline (BL): *$p<0.05$

	n	CV-Rapidly propagating CL300 msec	CV-Rapidly propagating 1000 msec	CV-Slowly propagating 300 msec	CV-Slowly propagating 1000 msec
BL	24	.50±.12	.47±.11	.23±.08	.22±.04
M	13	.43±.10*	.48±.10	.21±.09*	.23±.06
Q	11	.38±.07*	.38±.07*	.17±.05*	.17±.04*
M+Q	9	.30±.08*	.38±.05*	.17±.04*	.18±.03*

In the presence of drug(s), stimulation at short CL was interrupted for varying periods and recovery of CV evaluated. For M, τ_r was 206±83 msec and for M+Q 359±90. For Q alone, recovery was incomplete. Conclusions: (1) Over this range of CL, depression of CV by M was CL-dependent; (2) M+Q produced additional depression of CV over that of Q at shorter CL, but similar effects to Q at longer CL; (3) Depression of CV by drugs was orientation-independent; (4) τ_r for M was shorter than in vitro recovery of i_{Na}, and recovery with M+Q was slower than with M.

MONOPHASIC ACTION POTENTIALS DURING ATRIAL FLUTTER: EFFECTS OF PHARMACOLOGICAL INTERVENTIONS.

Kuei-Meng Wu, Ph.D., Samuel M. Ross, B.E.E., and Brian F. Hoffman, M.D., F.A.C.C. Department of Pharmacology, Columbia University, New York, NY 10032

Modification of Franz' electrode was developed to record monophasic action potentials (MAP) during persistent atrial flutter in anesthetized dogs. The tachycardia resulted from circus movement in the atrial tissues above the tricuspid ring. MAP were recorded from epicardium or endocardium during sinus rhythm, paced atrial rhythms and flutter. The recording electrode was a 1 mm diameter Ag-AgCl pellet anchored in the tip of a bell-shaped plaque or a malleable catheter. The indifferent Ag-AgCl electrode was situated in a recess 3-5 mm away from the recording electrode. Effective refractory period (ERP) was measured by suprathreshold stimuli applied at intervals of 8-10 cycles during paced rhythms at cycle lengths (CL) of 400-500 msec. When compared to records during sinus or paced rhythms MAP recorded during flutter at CL of 150-160 msec showed incomplete repolarization and a reduced rate of rise. Acetylcholine (ACh, 10-100 ug/kg) shortened MAP by up to 30%, increased take-off potential, decreased CL by 14% and converted flutter into fibrillation. Under 400 CL pacing, clofilium (0.5 mg/kg) increased MAP and ERP by 38% and 56%. During flutter, clofilium prolonged MAP by 34% and CL by 22% before the flutter was terminated. It is therefore concluded, with the aid of MAP analysis, that circus movement occuring in partially repolarized tissue around an anatomical barrier could be (1) accelerated by agents reducing action potential duration (APD)(ACh), (2) slowed and terminated by agents increasing APD (clofilium).

MECHANISMS UNDERLYING QUINIDINE-INDUCED INHIBITION OF THE SLOW INWARD CURRENT IN THE RABBIT ATRIOVENTRICULAR NODE

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Electrophysiologic mechanisms by which quinidine sulfate inhibits the slow inward current (i_s) were studied in the small preparations (0.2x0.2x0.1 mm) of the rabbit atrioventricular node. Voltage clamp studies using double microelectrode techniques revealed that the threshold concentration of quinidine to suppress the i_s was 1 µg/ml. At a therapeutic concentration of 5 µg/ml, the drug decreased the i_s from -44.0 to -30.7 nA and increased its inactivation time constant from 12.8 to 16.8 msec on depolarization from -40 to -10 mV ($P<0.01$, n=6). The steady-state inactivation curve for this current was shifted to more negative potentials by 2.8 mV ($P<0.05$, n=6). The fully activated i_s recorded at +10 mV measured -56.3 nA in control, and was decreased to -49.7 nA by quinidine. After a few minutes of clamping the membrane potential at -40 mV, quinidine exerted a tonic blocking action by decreasing the i_s from -41.7 to -31.7 nA. In the absence of quinidine, a positive current "staircase" of i_s was observed on sequential application of 10 depolarizing pulses of 2,000 msec. With 200 msec pulses, quinidine minimally reduced the i_s from -31.7 to -30.3 nA, whereas with 2,000 msec pulses, it progressively reduced the i_s from -30.0 to -23.2 nA, suggesting a use-dependent blockage of i_s. It is concluded that 1) quinidine exerts a potent blocking action on i_s by reducing its fully activated current and shifting the inactivation kinetics towards hyperpolarization and 2) the drug molecules bind to the i_s channel not only in the resting but also in the inactivated state.

VOLTAGE AND FREQUENCY DEPENDENT DEPRESSION OF MAXIMUM UPSTROKE VELOCITY BY FLECAINIDE ACETATE IN OVINE CARDIAC PURKINJE FIBERS

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Depression of maximum upstroke velocity (Vmax) by Type I antiarrhythmic drugs is modulated by both transmembrane voltage and frequency of stimulation. We studied the mechanism of Vmax depression by flecainide acetate (FA) in ovine cardiac Purkinje fibers using a double microelectrode voltage clamp technique. FA (5uM) shifted the steady state Vmax - membrane voltage relationship by 5.6 +2 mV in the hyperpolarizing direction. Affinity of FA for inactivated Na channels was studied by applying a depolarizing conditioning pulse (Vc) of varying duration and magnitude ending 200 msec before a test Vmax. Following long Vc, test Vmax was reduced by up to 30% in control and by up to 60% in the presence of FA. The slow inactivation process observed in the absence of drug was a bi-exponential process with time constants of 3.5 ± 0.9 sec and >90 sec. In the presence of FA a third phase of inactivation block was apparent with a time constant (19.8 ± 5 sec) intermediate to the two observed in control. Short Vc (<1 sec) produced minimal depression of Vmax consistent with both minimal binding of FA during the action potential (AP) upstroke and the long time constant for inactivation block. During AP trains, frequency dependent depression of Vmax was observed at all frequencies > 0.2 Hz. The time constant for depression of Vmax during trains was long (12.8 ±3 sec at 2 Hz) and recovery of Vmax from steady state depression was markedly prolonged (time constant of 29.5 ±8 sec). We conclude that the slow kinetics for both inactivation block and recovery from block results in depression of Vmax at all physiologic heart rates and may account for the marked slowing of conduction and proarrhythmic effects observed clinically with FA.

AMIODARONE: PREDICTORS OF CLINICAL RESPONSE IN REFRACTORY ATRIAL FLUTTER AND ATRIAL FIBRILLATION.

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The purpose of this study was to identify clinical response indicators for amiodarone(Amio) in the therapy of 40 patients(pts) with refractory atrial flutter(AFl) and atrial fibrillation(AFib) (21 chronic,19 paroxysmal). Initial Amio dosage was 800mg daily, tapered to 200-400mg daily. Underlying heart disease was ischemic in 16 pts, dilated cardiomyopathy in 12 pts, valvular in 6 pts, and idiopathic in 6 pts. Complete responders (CR)(28 pts,70%) reverted to sinus rhythm with abolition of symptoms for at least 3 consecutive mos.before checkup at 6-9 mos.; partial responders(PR) (6 pts,15%) had a major reduction in symptoms and/or 90% reduction in frequency of AFl or AFib;and non-responders(NR) (6 pts,15%) had minimal or no response. DC cardioversion was necessary in 5/13(38%) of the CR with chronic AFib,whereas medical reversion alone was effective in 8/13(62%) of this group. In 3/19(16%) pts with paroxysmal AFib or AFl,incessant AFl occurred after initiation of Amio and required cardioversion. Long term response to Amio was not predicted by age, duration of symptoms, dosage, height of F wave, ejection fraction, QTc, side effects, response of concomitant ventricular arrhythmias, etiology,or chronic vs. paroxysmal rhythm. However,left atrial(LA) size by M-mode echocardiography was greater($P<.001$) in the NR($\overline{5.4}$±.5cm) compared to the CR($\overline{4.2}$±.6cm) or the PR($\overline{4.0}$±.7 cm). 100% of pts with LA<4.6cm were CR or PR, whereas only 50% of pts with LA > $\overline{4.6}$ cm responded. We conclude:(1)Amio is highly effective (85% CR or PR) in controlling refractory AFib and AFl, and (2)LA dimension ≤ 4.6cm predicts efficacy.

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EFFECT OF FLECAINIDE ACETATE ON VENTRICULAR TACHYCARDIA INDUCTION AND VENTRICULAR FIBRILLATION PREVENTION IN A CONSCIOUS CANINE MODEL OF SUDDEN DEATH.

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The efficacy of flecainide acetate (FA) in preventing post-infarction ventricular tachycardia (VT) induction and ischemic ventricular fibrillation was evaluated in a conscious canine model of sudden death. An anterior wall myocardial infarction (MI) was created by 2-hour occlusion followed by reperfusion of the left anterior descending coronary artery of 15 dogs. All dogs had VT reproducibly inducible 5±1 days after MI by programmed ventricular stimulation using a maximum of 3 extrastimuli. A loading dose of intravenous FA, 2 mg/kg over 20 min, was administered to 7 dogs (group A) and normal saline to 8 dogs (group B). VT remained inducible in 7/7 group A and 7/8 group B dogs. In both groups, there was no significant change of VT cycle length (160±8 ms vs. 172±12 ms in group A, 189±10 ms vs. 195±12 ms in group B) or in ventricular refractoriness (147±6 ms vs. 147±5 ms in group A, 169±8 ms vs. 159±11 ms in group B). With maintenance intravenous FA, 1 mg/kg/hr for 4 hrs, to group A and normal saline to group B, ischemic ventricular fibrillation, resulting in sudden death, occurred in 6/7 dogs in group A and 8/8 dogs in group B. The mean time to sudden death was 218±109 min in group A and 396±86 min in group B. There was no significant difference between MI size in group A (26±3% of left ventricle mass) and group B (22±3% of left ventricle mass).

Thus, during the early recovery period after MI, FA does not prevent VT induction by programmed ventricular stimulation nor occurrence of ischemic ventricular fibrillation in a conscious canine model of sudden death.

THALLIUM KINETICS IN REPERFUSED INFARCTS: DIFFERENTIAL EFFECT OF RESIDUAL STENOSIS.

Andrew M. Grunwald, M.D., F.A.C.C., Joseph Wiesel, Bruce Robin, Monty M. Bodenheimer, M.D., F.A.C.C. Long Island Jewish Medical Center, New Hyde Park, New York.

Thallium (Tl) scans are commonly used to assess myocardial salvage following reperfusion (REP) of an occluded artery to a jeopardized region. To examine Tl kinetics in reperfused infarct zones, a balloon occluder (BO) on the circumflex artery in 6 dogs was inflated for 3-4 hours and then deflated. After 3 weeks' recovery the dogs underwent serial Tl scans during isoproternol (ISP) and a week later during persantine (PER) infusion. Following intravenous administration of Tl, anesthetized dogs were imaged in the LAO projection for 3 hours without movement. Three weeks later 5 of the dogs underwent serial Tl scans following intracoronary infusion (IC) to assess intrinsic washout. After 1 hour of serial images in the LAO projection, the occluder was inflated (I) and serial images were again obtained. Dogs were sacrificed and infarction confirmed at autopsy. Tl uptake in the REP infarct zone was 85 ±6% of that seen in the normal septum. The % washout: *p=NS **p=.005

	ISP*	PER*	IC-Tl*	IC-Tl-BOI**
REP infart %	14±8	18±6	32±16	18±12
Normal septum	15±10	17±12	31±17	28±10

Thus (1) Tl uptake in REP infarct zones is reduced by only 15%; (2) where myocardium is perfused by widely patent arteries Tl washout cannot differentiate between infarct and normal zones; (3) reduced Tl washout in REP zones suggests continued hypoperfusion of the jeopardized region.

Tuesday, March 11, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 10:00AM–11:00AM
Hall D, Georgia World Congress Center
Myocardial Infarction—Experimental

PARADOXICAL LACTATE PRODUCTION DURING REPERFUSION OF ISCHEMIC MYOCARDIUM.

Edward N. Dean, M.D., Thomas M. Annesley, M.D., Thomas R. Underwood, David A. Canvasser, D.V.M., John M. Nicklas, M.D. University of Michigan, Ann Arbor, Michigan.

Lactate is extracted by normal myocytes and produced when cells become ischemic. To determine the effects of reperfusion on reversibly and irreversibly injured post-ischemic myocardium, regional lactate metabolism was measured in open-chest anesthetized dogs. Percent net lactate extraction was determined between the carotid artery and great cardiac vein before, at the end of either a 15 minute (n=8) or 4 hour (n=5) left anterior descending coronary artery occlusion, and at 30 and 120 minutes post-reperfusion. Results (mean ± SE):

PERCENT LACTATE EXTRACTION

	Baseline	Occlusion	30" Post	120" Post
15 min	41 ± 5	-44 ± 39+	30 ± 8	36 ± 6
4 hr	37 ± 13	22 ± 14	-73 ± 11+	-18 ± 16+

+ difference from baseline, $p < 0.05$

Therefore, in reversibly injured myocardium, lactate production is rapidly replaced by extraction during reperfusion. In contrast, by the end of 4 hr of coronary occlusion, net lactate production has already been replaced by extraction. Reperfusion of this irreversibly injured, infarcted tissue paradoxically leads to renewed lactate production. This suggests that reperfusion of areas of infarcted myocardium can unveil or induce further ischemia as indexed by lactate production.

LATENT MYOCARDIAL DYSFUNCTION AFTER BRIEF CORONARY OCCLUSION.

Erwin Schröder MD, Robert Kieso MS, Michelle Hunt BS, Marie Schröder MD, Donald Laughlin MSEE, Birgit Grimlund, Richard Kerber MD, FACC, U of Ia, Iowa city, Ia

After brief (5 mins) periods of coronary artery occlusion followed by reperfusion, myocardium appears to recover fully within 1 hour. Our hypothesis was that such myocardium has prolonged latent dysfunction which would become evident when the reperfused myocardium was challenged by a second coronary occlusion. This hypothesis is clinically relevant because multiple ischemic episodes often occur over short time periods. We studied 16 open-chest dogs with controlled heart rate and arterial pressure. Regional myocardial function was assessed by measuring systolic wall thickening (WTh) every 5 secs; WTh was displayed continuously by a new 5 Mz miniaturized echo transducer, fixed to the epicardium by suction. All dogs underwent an initial challenge (Challenge 1) of 30 secs of coronary occlusion (CO). Thereafter the control group (n=5) underwent no intervention during the next 90 mins, while the study group (n=11) underwent 5 mins CO and 90 mins reperfusion. All dogs were rechallenged by 30 secs CO after 30 mins (Challenge 2) and 90 mins reperfusion. Results at 30 mins of reperfusion (*=p<.05 Challenge 2 vs. Challenge 1) (WTh expressed as mean):

		Time (Seconds) During Challenge Coronary Occlusion									
Group		0"		5"		10"		20"		30"	
Challenge #		1	2	1	2	1	2	1	2	1	2
Control	WTh(%)	61	54	36	45	3	9	-6	-14	-8	-8
5' CO	WTh(%)	56	55	54	17*	17	-9*	3	-11*	-9	-15

These changes persisted during a third challenge at 90 mins of reperfusion. Conclusion: After coronary occlusion (5 mins) and up to 90 mins of reperfusion, apparently normal systolic thickening deteriorates more quickly in response to a challenge coronary occlusion. This suggests the presence of prolonged latent myocardial dysfunction.

DOES LEFT VENTRICULAR RUPTURE THRESHOLD AFTER MYOCARDIAL INFARCTION IN THE DOG MEASURE ADEQUACY OF HEALING?
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The mechanical resistance of the infarcted LV to rupture, or rupture threshold (RT), might be a measure of adequacy of healing after acute myocardial infarction. The temporal changes in infarct hydroxyproline (OHP;spectrophotometry; mg/Kg), LV topography (computerassisted analysis of papillary short-axis two-dimensional echocardiographic images obtained pre-sacrifice) and RT (balloon technique) were measured in 50 dogs with left anterior descending coronary artery occlusion: 17 controls (10 no infarcts and 7 dying < 1 hour postocclusion); 40 infarcts from dogs killed between 2 and 42 days. Another 15 dogs were given low dose nitroglycerin (NG) or ibuprofen (IBU; 6.25 mg/Kg/hr) for 6 hours after occlusion and parameters measured at 7 days: 10 infarcts, 5 NG, 5 IBU. The thinning ratio (TR, infarct/normal wall thickness) and expansion index (EI, infarct/non-infarct segment length) were computed. Results were:

Group	n	RT(mmHg)	OHP(mg/Kg)	TR	EI
Controls	17	1213	4.7	1.0	1.0
2-4 days	12	878*	4.7	0.9	1.2*
7 days	5	860*	10.0*	0.9	1.2*
14 days	4	973*	18.4*	0.9	1.2*
28 days	2	595*	44.2*	0.7*	1.2*
42 days	10	594*	48.8*	0.5*	1.3*
NG,7 days	5	720*	11.8*	0.9	1.1
IBU,7 days	5	397*†	10.1*	0.8*	1.3*

*p<0.05 vs control; † p<0.05 vs untreated 7 day group. Thus,infarct healing is associated with 1)early expansion and late thinning, 2) progressive rise in OHP between 7 days and 6 weeks, and 3) a mild early decrease and a marked late decrease in RT. IBU, but not NG,caused early thinning with a lower RT, suggesting inadequate healing.

ARE REGIONS OF DELAYED ACTIVATION DURING A BASIC RHYTHM THE RESPONSIBLE ARRHYTHMOGENIC SUBSTRATE FOR REENTRY?
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Late potentials (LP) as detected by body surface signal averaging (SA) techniques may indicate susceptibility to reentrant ventricular rhythms (RVR). Using a computerized multiplexer system and a high resolution SA system, we compared the activation times (AT) at 62 epicardial sites with LP in 3 orthogonal SA leads. The SA ECGs were recorded at a gain of 35000 at filter settings of 80 to 300Hz for 100-300 beats. Noise levels were on the order of .5 microvolts or less. RVRs were induced by programmed stimulation in canine hearts 3-5 days post infarction and appeared as two circulating wavefronts traveling around an arc of functional conduction block. Only those hearts where the final common reentrant pathway (FCRP) was identified in a thin surviving epicardial layer were examined. In 7 of 9 experiments, SA during basic rhythm (BR), sinus or S_1-S_1 pacing: 400-500 msec, detected LP which corresponded temporally with the region of latest epicardial AT. Subsequent SA of RVR initiation revealed that sites of LP during a BR were not always responsible for LP detected in the S_2-V_1 interval. Examination of activation maps for these beats confirmed that the region responsible for LP during BR were not part of the FCRP during reentry. Regions of marked delay or 2:1 conduction during the BR usually blocked during S_2 and did not participate in the reentrant process. In conclusion, late potentials detected during a basic rhythm may be associated with reentrant arrhythmias. However, the region responsible for delayed activation during basic beats may not always participate in the reentrant pathway.

METABOLIC BASIS FOR HETEROGENOUS NORADRENALINE RELEASE DURING MYOCARDIAL ISCHAEMIA.
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Denervation studies have shown that non-reflex (i.e. local) release of noradrenaline (NA) is important for the production of ventricular fibrillation during myocardial ischaemia and studies with stop flow ischaemia showed that local NA release, detected during reperfusion, can be inhibited by agents which normally block neuronal NA uptake (eg desipramine, DMI). The metabolic prerequisites for this release have now been studied in two further models of the isolated perfused rat heart. Global low flow (5%) ischaemia with normoxic perfusate does not lead to increased (vs control) overflow during 40min ischaemia (n=7). However following 60min substrate-free preperfusion 5% ischaemia produces an enhanced overflow with NA concentrations (at 25min ischaemia) of 51.4±7.4 in a control (n=8) and 21.8±1.8pmol/ml in a DMI treated group (n=8). In a second model anoxic perfusion (pO_2<1mmHg) was used at normal flow rate without added substrate (n=6), without substrate but with DMI (n=6) or with 11mM glucose (n=6). NA concentrations in pre-anoxic samples were <0.5 pmol/ml. In the anoxic no substrate series NA concentrations were 7.3±0.7 (20min), 15.1±1.5 (30min) and 15.5±0.5 pmol/ml (40min) whereas in the DMI group respective values were 2.5±0.3, 3.1±0.2, and 5.3±0.9. 11mM glucose suppressed NA overflow at all times. The results support the concept that NA efflux occurs using the same carrier as normally permits neuronal NA uptake. The metabolic conditions required suggest that in vivo such release would be limited to areas of severe flow reduction producing markedly heterogenous NA stimulation - a potentially potent arrhythmic insult.

DEPRESSION OF LEFT BUNDLE AUTOMATICITY AFTER CORONARY ARTERY OCCLUSION AND REPERFUSION.
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His-Purkinje automaticity was assessed in the normal canine heart and at 1, 3, and 7 days after temporary anterior descending coronary artery occlusion (CAO). Automaticity was evaluated in vivo (vagus nerve stimulation) and in vitro (superfused His-Purkinje system) (see table). Under control conditions, the idioventricular rhythm (IVR) originated most commonly in the proximal left bundle (PLB). One, 3, and 7 days after CAO (30 min), the site of IVR formation had shifted to the right

IN VIVO	**CONTROL**	**DAY 1**	**DAY 3**	**DAY 7**
IVR (bpm)	45±2	30±3*	45±3	56±3
PLB origin	73%	0%**	0%**	0%*
*p<0.05	(N=15)	(N=13)	(N=14)	(N=3)
IN VITRO	**CONTROL**	**DAY 1**	**DAY 3**	**DAY 7**
PLB (bpm)	40±3	1±2**	20±8**	21±9
10-6M Epi	146±18	10±6**	52±9**	54±9*
PLB origin	75%	0%*	33%	0%
**p<0.01	(N=8)	(N=9)	(N=6)	(N=3)

bundle and His-bundle. On day 1, right bundle automaticity was also depressed. A decreased response to epinephrine was observed in the PLB as late as 7 days post-CAO. Neither the rate (39±4 bpm) nor the site (57% PLB; N=7) of the IVR was depressed 24 hr after 15 min of CAO. Necrosis in the anterior wall (1.5±0.8 gm) was present after 30 min, but not 15 min of CAO. The PLB function may be impaired by toxic substances released from the distantly injured myocardium.

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EFFECTS OF ISCHEMIA AND REPERFUSION: A COMPARISON OF ISOLATED BUFFER AND BLOOD PERFUSED HEARTS.

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Most studies using isolated hearts have utilized Krebs buffer as coronary perfusate. However, recent work has suggested that oxygen free radicals, generated from leucocytes, and serum complement, may contribute to ischemic-reperfusion injury. To study this issue, we compared the effects of 15 min complete global ischemia and 60 min reperfusion at 37°C in isolated isovolumic (ballon-in-LV) rabbit hearts paced at 180/min and perfused with either Krebs-Henseleit buffer (KHB) (n=9) or fresh whole rabbit blood (BLD) (n=15). Coronary perfusion pressure was held constant at 80mmHg during pre-and post-ischemia in both groups. BLD perfusion resulted in a physiologic perfusion rate of 1.5±0.7ml/min/gm compared to 10.5±0.8ml/min/gm ($P<0.01$) with KHB. Pre-ischemic performance was comparable in the 2 groups; developed pressure/EDP was 90±3/11±1mmHg vs 96±6/10±1mmHg for BLD vs KHB. The BLD group had greater ischemic-reperfusion injury than the KHB group. At end-ischemia both groups were asystolic, but the BLD group had more severe contracture (LVEDP=49±mmHg) than the KHB group (LVEDP=15±5mmHg, $P<.001$). After 60 min of reperfusion, developed pressure was 66±6% of pre-ischemia KHB, but only 44±5% in the BLD group ($P<0.05$). Contracture at end-reperfusion was greater in the BLD group: LVEDP=37±6 vs 18±4mmHg, $P<0.05$), for BLD vs KHB. However, the wet/dry weight ratio was greater in the KHB vs BLD group (7.3±0.2 vs 5.0±0.1, $P<0.001$), and perfusion during reperfusion was not reduced relative to pre-ischemia with BLD, but decreased by 23% ($P<0.01$) with KHB. Conclusion: Ischemic-reperfusion injury, manifested by a greater loss of contractile function and greater contracture, was worse in the BLD group than in the KHB group, despite more edema and an increase in coronary resistance post-ischemia in the latter. Studies with buffer-perfused hearts may underestimate the degree of damage caused by an episode of ischemia and reperfusion in vivo, because the buffer perfusate lacks elements which contribute significantly to ischemic-reperfusion injury.

DELINEATION OF THE CHARACTER AND OXIDATIVE LIMITS OF MYOCARDIAL PERI-ISCHEMIC BORDERZONE.

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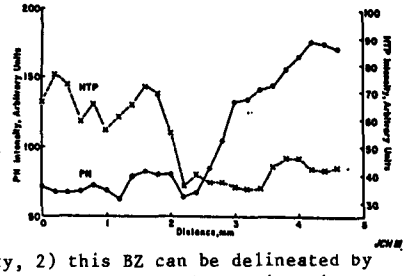
Although the peri-ischemic borderzone (BZ) is narrow, it probably provides the substrates of slow conduction and refractoriness essential for re-entrant arrhythmias. The purposes of this study were: 1) to determine the distance between perfused and ischemic myocardium using a marker dye, hematoporphyrin (HTP) and 2) to characterize the tissue oxidative levels within this peri-ischemic BZ. A coronary artery in the ventricular free wall was ligated in rabbit heart perfused with oxygenated HTP on a modified Langendorff apparatus. Hearts were then freeze-clamped to preserve the spatial integrity of the perfused/ischemic BZ and perfusion assessed by fluorescence photography (HTP >600 nm) and ischemia by scanning tissue fluorometry (NADH 430-510 nm).The HTP signal changes gradually from high to low and the NADH signal from low to high over~500 microns. We conclude: 1) flow across the BZ of an experimental infarct has two states, "high" and "normal" vs. "low" and insufficient to sustain cell viability, 2) this BZ can be delineated by marker dye fluorescence photography and scanning microfluorometry, 3) the BZ transition occurs over ≤ 500 microns, 4) within the BZ are intermediate tissue oxidative levels that may predispose to the slow conduction and refractoriness necessary for re-entrant arrhythmias.



POST-INFARCTION ANEURYSM FORMATION: EFFECT OF EARLY AND LATE INCREASES IN STRESS.

Carolyn M. Connelly, Ph.D., Robert J. McLaughlin, Ph.D., W. Mark Vogel, Ph.D., William N. Grice, Carl S. Apstein, M.D., FACC. Boston University School of Medicine, Boston, MA

Post-myocardial infarction (MI) aneurysm formation is a complication which greatly increases morbidity and mortality; however, the basic factors which cause aneursym formation have not been defined. We assessed the effect of post-MI scar maturity on a scar's ability to withstand an imposed load (stress) without undergoing an irreversible increase in length (strain), since such a length increase represents the initial step in aneurysm formation.

Post-MI aneurysm formation was studied in 20 rabbits using excised strips of acutely infarcted (24 hrs) or healing (3-4 wks) post-MI scar tissue. Strips were repetitively stretched for 1 hr at 4Hz between peak (systolic) and resting (diastolic) stresses of 2 and 0.2g/mm^2, simulating LV pressures of 80/8mmHg. During a 2nd hr, these stresses were maintained (controls, C) or afterload was increased (↑AL) to a peak stress of 6g/mm^2 (240mmHg). During a 3rd hr all strips were returned to initial conditions. Results are expressed as % increase in strip length (L) at peak "systolic" stress relative to the strip length at 1 hr (L_o); $(L-L_o)/L_o \times 100$ ± SEM.)

	Acute Infarct		3-4 Week Scar	
	C(n=5)	↑AL(n=5)	C(n=5)	↑AL(n=5)
2nd hr	0.2±0.1	4.2±1.2*	0.5±0.1	4.7±0.7*
3rd hr	0.3±0.1	3.5±1.3*	0.8±0.2	3.9±0.6*

*$p<0.05$ for ↑AL vs C.

Conclusion: ↑AL for 60 min caused a comparable length increase (2nd hr) in acute infarct and 3-4 wk scars, which did not reverse with strip unloading (3rd hr). ↑AL may predispose to aneurysm formation both early and late after an MI.

Tuesday, March 11, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 11:00AM–12:00NOON
Hall D, Georgia World Congress Center
Myocardial Metabolism

ISOENZYME DISTRIBUTION IN OVERLOADED HUMAN ATRIAL TISSUE:

Peter Buttrick, M.D., Ashwani Malhotra, Ph.D., Lucille McDermott, Lillian Lam, and Richard Brodman, M.D. Division of Cardiology, Montefiore Hospital, Albert Einstein College of Medicine, Bronx NY.

Distinct myosin isoenzymes have been identified in mammalian hearts and reflect the imposed load and the contractile state of the cardiac muscle. In rats, systolic overload shifts the normal V_1 predominant isoenzyme pattern to V_3. In human ventricular tissue,V_3 predominates and analogous isoenzyme shifts have been difficult to identify. Human atrial tissue has equimolar V_1 and V_3. We studied the isoenzyme distribution in pressure and volume overloaded human atrial appendages (LAA, RAA) obtained at the time of valve replacement. (MS, mitral stenosis; MR, mitral regurgitation). Isoenzyme distribution was determined in crude myosin extracts by nondenaturing pyrophosphate gel electrophoresis.

% V_3	Age	LAA	RAA(-)PHTN	RAA(+)PHTN
Control	49±13(3)	45±7(3)	-	-
MS	54±18(9)	76±11(8)*+	51±4 (4)	73±18(4)+
MR	51±13(5)	69±16(5)*+	49±2 (4)	-

(Mean ± SD; (n); PHTN, pulmonary hypertension; *$p<0.05$ vs Control, +$p<0.05$ vs RAA(-)PHTN,)

No clear relationship could be established between the severity of the valvular disease and the isoenzyme shift, although all patients had long-standing symptomatic disease.In one patient with acute MR 2° to papillary muscle rupture, no increase in V_3 was seen in LAA. These data show that human atrial tissue can increase %V_3 in response to chronic pressure and/or volume overload and imply that the tissue has the capacity to alter its genetic expression in response to a pathologic load.

LYMPHOCYTE BETA-ADRENERGIC-RECEPTOR DENSITY AND PLASMA CATECHOLAMINES IN ACUTE MYOCARDIAL INFARCTION.

Babeth Rabinowitz, M.D., F.A.C.C., Moshe Herskowitz, Ph.D., Ella Elazar, M.Sc., Hanoch Hod, M.D. and Henry N. Neufeld, M.D., F.A.C.C., Heart Institute, Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv University, Israel.

Although significant changes in plasma catecholamines (CA) have been previously demonstrated in acute myocardial infarction (AMI) by us and others, little is known about the beta-adrenergic receptor density (β-density) during the course of AMI. Fifteen patients with definite AMI, who did not receive therapy with beta agonists or antagonists, were studied. Lymphocyte β-density in fmol/mg. protein was measured during the 1st, 2nd and 7th day after onset of AMI, along with plasma CA. Mean ± SEM of β-density, CA, heart rate (HR) and blood pressure (BP) are the following:

Days	β/density	CA	HR	BP
1st	75.2±10	599±70	108±9	100±14
2nd	20.1± 8	407±68	100±7	98± 9
7th	18.5± 8	312±35	72±4	90± 9

Fifteen noncardiac patients (controls) had β density 31±8. The patients with anterior MI had more β-receptors than those with inferior MI. β-density was not increased in 3 patients who received streptokinase.

The physiopathologic significance of the above findings in relation to the clinical course and the therapeutic interventions is currently investigated.

The results demonstrate, therefore a high β-density in the first 24 hours of AMI, which could be partially correlated with CA levels and the hemodynamic parameters of HR and AP. The β-density measured in lymphocytes may thus serve as a simple marker of sympathetic activity in patients with AMI.

MYOCARDIAL "BIOCHEMISTRY" IN CLOSED CHEST ANIMALS.

M. Osbakken, L. Ligeti, M. Sohnall, L. Bolinger, H. Subramanian, J. Leigh, and B. Chance, Biochemistry/Biophysics, University of Pennsylvania, Philadelphia, PA 19104.

Cardiac anatomy can be evaluated with a number of imaging modalities, including Magnetic Resonance Imaging. However, in vivo study of cardiac metabolism related to mechanical function is more difficult and not done routinely. Methods to study high energy phosphate metabolism using ^{31}P NMR in closed chest dogs were developed. External surface coils were placed over surgically prepared "cardiac windows" in 3 dogs. ^{31}P NMR spectra were obtained (6-8 minute scans with S/N = 5:1) during control, hypoxic (P_aO_2 = 20 Torr), and hypertensive (methoxamine infusion to pressures of 300/200 mm Hg) conditions and after successful resuscitation from cardiac arrest. The relationship between Pi/PCr (measure of phosphorylation potential) and cardiac "work" (Heart rate x Blood pressure) was used as a measure of metabolic state of the heart. Pi/PCr ratios increased with all interventions: control = 0.54; hypoxia = 1.42; hypertension = 1.5; post arrest = 1.5. The increase in Pi/PCr was associated with increased "work" in the hypertensive state, ($1.5x10^4 \rightarrow 2.8x10^4$) while hypoxia ($1.2x10^4 \rightarrow 1.8x10^4$) and post arrest ($1.3x10^4 \rightarrow 1.5x10^4$) were associated with variable work load. This indicates that the more extreme work load of the hypertensive state induces maximal velocity (V^{max}) of phosphorylation (ATP synthesis). The velocity of phosphorylation is far from V_{max} in hypoxia. In the post arrest state, there is apparent dissociation of work and Pi/PCr, indicating a loss in metabolic control.

ALTERED ENERGY METABOLISM IN HEARTS FROM SPONTANEOUSLY DIABETIC BB/W RATS.

Heinrich Taegtmeyer, M.D.,D.Phil,F.A.C.C., Raymond R. Russell III, B.Sc., Angela L. Silvestain, B.Sc., University of Texas Medical School, Houston, Texas.

In order to assess the effect of acute diabetic ketosis on the heart we studied cardiac function and metabolism in spontaneously diabetic BB/W rats and compared data to non-diabetic litter mates. Plasma metabolite levels were as follows (*p <0.01):

	Glucose	3-Hydroxy-butyrate	Aceto-acetate
Non-diabetic (N=10)	10.1	0.28	0.07
Diabetic (N=32)	23.3*	3.85*	0.95*

Hearts were freeze-clamped in situ for analysis of metabolites and enzyme activities. Tissue contents of 2-oxoglutarate (1.14 vs. 0.27), glutamate (20.6 vs. 14.2), lactate (8.47 vs. 2.79) and pyruvate (1.87 vs. 0.49), were increased in diabetic vs. control hearts (all values µmol/g dry, p<0.05). Activities of 2-oxoglutarate dehydrogenase and lactate dehydrogenase were the same in both groups. Activities of acetoacetyl-CoA thiolase (339 vs. 18, p<0.001) and of 3-hydroxybutyrate dehydrogenase (114 vs. 52, p<0.05) were higher, while activities of phosphorylase (27 vs. 57, p<0.05) and hexokinase (37 vs. 98, p<0.05) were lower in diabetic than in control hearts (values: µmol/min/g wet). When hearts were perfused as working hearts, intrinsic left ventricular function, measured by constructing Frank-Starling curves, was the same in both groups. The data indicate metabolic adaptation favoring the oxidation of ketone bodies, inhibition of pyruvate oxidation and a possible impairment of the 2-oxoglutarate dehydrogenase reaction in hearts from diabetic animals.

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SYSTOLIC MYOCARDIAL STIFFNESS: A NEW CONCEPT IN THE DEVELOPMENT OF THE END SYSTOLIC PRESSURE VOLUME RELATION.

Israel Mirsky, Ph.D., F.A.C.C., Tsukasa Tajimi, M.D., and Kirk L. Peterson, M.D., F.A.C.C., Brigham and Women's Hospital, Boston, MA.

The end systolic pressure-volume relation (ESPVR) and zero stress volume (V_o) are derived on the basis of the new concept of systolic myocardial stiffness (SMS). Five dogs were instrumented with micromanometers and sonomicrometers (LV long and short axes and wall thickness) for volume (V) and stress (σ) calculations. SMS = $KV d\sigma/dV$ (K, a geometric factor) was computed from peak σ to near end ejection in control (C), angiotensin II (AT), phenylephrine (PE), caval occlusion (CA) and nitroprusside states at constant heart rate. Integration of the SMS equation yielded the ESPVR: $\sigma = GP = (SMS/K) \log (V/V_o)$ where $G = \alpha + \beta V$, $V_o = V_c \exp(-K\sigma_c/SMS_c)$ and subscript c denotes control state values at end systole.

	SMSm	σm*	SMSpv	σpv†
C	248±32	191±18	221±34	136±9
AT	241±18	250±30	233±20	240±23
PE	263±17	255±37	235±21	224±47
CA	246±31	175±18	232±32	139±11
NP	216±31	122±7	210±34	112±7

V_{om} = 13±2; V_{opv} = 11±2.

* F (4,20) = 5.39; P< 0.005; F(4,20) = 5.64, P< 0.005

m = max. σm = σ at SMSm; PV = at (P/V)max.

We conclude 1. SMS is independent of stress, hence may be useful for detecting changes in myocardial contractility. 2. ESPVR is curvilinear, therefore Emax is not constant. 3. V_o is always positive and may have clinical value in an estimation of the theoretical maximum ejection fraction at zero afterload.

MEASURES OF REGIONAL FUNCTION IN VENTRICLES WITH HETEROGENEOUS CONTRACTILE STATE.

Thomas Aversano M.D., W. Lowell Maughan M.D., Lewis C. Becker M.D. FACC. Johns Hopkins University, Baltimore, MD

This study tested the hypothesis that the end-systolic pressure-thickness relation (ESPTR) is a better measure of regional function than percent wall thickening (%ΔT) in the ventricle with regional differences in inotropic state. Six dogs were instrumented with an LV pressure transducer and sonomicrometer crystals in the left anterior descending (LAD) and circumflex (LC) regions for measurement of wall thickness (WT). The ESPTR, defined by a slope, Ees, and thickness-axis intercept (T0), was obtained during caval occlusion. To calculate %ΔT, end-systolic thickness (EST) was defined as WT occuring 20 msec prior to peak negative LV dP/dt. For the ESPTR, end-systole was defined as occuring when the slope of the ESPTR (Ees) was maximal. Measurements were made before (C) and during intracoronary infusion of dobutamine (D) into the LC. The LAD-region ESPTR and %ΔT showed no change with LC D infusion. Below are LC-region data:

	EDT (mm)	EST (mm)	%ΔT	Ees (mmHg/mm)	T0 (mm)
C	11.6	12.9	10.8	-55	14.9
D	12.5*	14.1*	11.9	-183*	15.6

(* = P<.05 vs control; EDT=end-diastolic WT)

The LC-region ESPTR shifted rightward with D, indicating positive inotropy, while the standard dimension change measure, %ΔT, failed to detect any effect of D on regional LC function. LC-region %ΔT failed to change in part because preload decreased (increased EDT). In addition, LC D infusion produced regional differences in timing of end-systole and thus altered the relation between LV dP/dt and regional end-systole. As a result, EST in the LC region was measured at a time later than actual local end-systole. Using the ESPTR, end-systole occured 137 msec after onset-systole in the LC region and 180 msec after onset-systole in the LAD region, while end-systole for the ventricle as a whole (20 msec before peak negative LV dP/dt) occured 190 msec after onset-systole. By measuring EST at this later time, %ΔT is underestimated and fails to increase with D. We conclude that the ESPTR is a better measure of regional function than %ΔT, since it is load-independent and does not use a global parameter to time regional end-systole.

MECHANISM OF VENTRICULAR WALL MOTION ASYNCHRONY IN HYPOKINETIC MYOCARDIAL SEGMENTS.

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The early systolic bulge and early diastolic shortening noted in hypokinetic segments (Hypo) despite retained total systolic shortening was analyzed in chronically instrumented dogs with digitized sonomicrometric data. Using a model in which cardiac contraction was viewed as time-varying elastance (Elas), instantaneous tension (T) related to segment length (L) by the exponential relation: $T=\exp(\alpha L+\beta)$. T was independently obtained by instantaneous internal diameter and pressure. α is a time-varying elastic constant, calculated every 1 msec. In diastasis, α and β were unchanged (SD of α=1% of mean). α was then plotted against time over the cardiac cycle. During control, α increased from end-diastole reaching maximum (45+5% increase) at end-systole with constant β. To model Hypo induced by coronary occlusion the time course of α was the same as pre-occlusion, but the value was lower at each point in time. L over time was derived from the above equation using measured T creating a typical asynchronous motion (Async) curve seen in Hypo. Load variation changed L motion, but with constant time sequence of α. Elas approximated by a linear equation cannot explain this Async. Derived L correlated with measured L in Hypo (r=.97). Conclusion: The Async of ischemic myocardium is not due to an asynchronous active state but due to decreased contractility and the elastic property of ischemic myocardium. Exponential approximation of changing Elas describes regional function better than a linear model.

THE RATE OF MYOCARDIAL VOLUME LOADING AND REGIONAL END-SYSTOLIC HYSTERESIS IN INTACT HEARTS.

William P. Miller, M.D., F.A.C.C., Stephen H. Nellis, Ph.D., and A. James Liedtke, M.D., F.A.C.C. Section of Cardiology, University of Wisconsin, Madison, WI.

We have previously shown that systolic LVP-segment length relationships in intact hearts show hysteresis. To determine the effect of the rate of myocardial stretch on the magnitude of this hysteresis, 8 paced, extracorporeally perfused pig hearts were treated with IV propranolol (1 mg /kg) and atropine (0.1 mg/kg). Simultaneous LVP, myocardial wall thickness (Th) and two perpendicular segment lengths (SLL, SLC) were measured in consecutive, variably loaded beats obtained by the LV injection of blood at fixed rates (R). Randomized trials of infusions at R1 (56±2 ml/sec) vs R2 (27±2 ml/sec, P < 0.001) resulted in nearly identical maximal changes in peak LVP (116±4 to 147±4 vs 118±4 to 152±4 mm Hg), LVEDP (7.6±0.5 to 12.2±1.4 vs 7.1±0.4 to 11.2±0.9 mm Hg), Th (13.7±1.4 to 12.5±1.4 vs 13.9±1.3 to 12.4±1.2 mm), SLL (15.6±1.3 to 16.4±1.4 vs 15.4±1.2 to 16.4±1.4 mm), SLC (11.3±0.7 to 11.9±0.7 vs 11.1±0.7 to 11.9±0.8 mm). These similar changes however, occurred over 2-3 beats at R1 vs 5-7 beats at R2 (P < 0.001). Using end- shortening to approximate end-systole (ES), ESLVP-length relationships obtained at the same time from the R wave in each cardiac cycle showed hysteresis. The area of the hysteresis loops increased 97% in ESLVP-Th (P < 0.025), 89% in ESLVP-SLL (P < 0.01), and 68% in ESLVP-SLC (P < 0.05), being significantly greater at the slower rates of loading (R2). These data show that the myocardium of the intact ventricle has a beat-to-beat memory that is dependent on the rate of myocardial stretch and this may represent length dependent activation in the intact heart.

RIGHT VENTRICULAR DYSFUNCTION AFTER REVERSAL OF SEVERE PRESSURE OVERLOAD IN THE CAT

Thomas Wisenbaugh, M.D., Dale Paley, George Yu, William N. O'Connor, M.D., University of Kentucky and VA Medical Centers, Lexington, Kentucky

Removal of pressure overload(PO) before the onset of congestive failure(CHF) reverses hypertrophy and contractile dysfunction in the cat right ventricle(RV). However, the reversibility of hypertrophy and dysfunction long after removal of a PO severe enough to cause CHF has not been studied. We therefore measured RV mass(M) and function in 6 cats 8-10 months after relief of severe PO produced by pulmonary artery banding for 2 months. RVP (72±19 mmHg) returned to normal (21±3 vs 26±4 for control) after band removal. Stroke(S) work(W), indexed(I) for RVM was determined from electro-magnetic flow and mean systolic P at 8 mm filling P.

(mean+STD, *p 0.05 vs C)

	Body M(kg)	RVM(g)	RV:LVM	SWI
C	4.29	2.06	.23	40.6
(n=6)	±.54	±.37	±.03	13.9
PO	4.00	3.71*	.40*	13.1*
(n=6)	±.96	±.93	±.07	±3.8
Reversal	4.64	2.98*	.39*	11.4*
(n=5)	±1.55	±.46	±.06	±5.3

RV mass remained susbstantially elevated and stroke work per gram of RV remained significantly depressed 8-10 months after pressure overload was completely reversed. Thus, as previously observed in patients treated surgically for valve disease, ventricular hypertrophy and pump dysfunction may persist long after reversal of a severe pressure overload.

THE INOTROPIC AGENT AMRINONE DOES NOT INCREASE MYOCARDIAL INFARCT SIZE

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It is often necessary to administer inotropic agents to patients with acute myocardial infarctions who have heart failure, but there is often concern that such agents can extend the infarct. Previous studies showed that amrinone increases epicardial S-T segment elevation and intramyocardial pCO_2 during brief periods of myocardial ischemia; however, whether amrinone actually increases anatomic infarct size is unknown. Anesthetized dogs were subjected to 3 hours of coronary artery occlusion and 3 hours of reperfusion. At 30 minutes post coronary artery occlusion, dogs were randomized to receive either saline (n=9) or amrinone (n=9; 1mg/kg bolus followed by 6mg/kg/hr) for 3 hours. Area at risk (AR), determined using monastral dye, was 19.7±2.6% in control dogs and 20.2±1.8% in amrinone-treated dogs (p=NS). Area of necrosis (AN), assessed by tetrazolium stain and expressed as % AR, was 60.6±6.1% in control and 54.6±5.6% in amrinone group (p=NS). Preocclusion, LVEDP was 11±1 mmHg and increased after coronary artery occlusion, but before therapy, to 20±3 mmHg in controls and to 17±1 mmHg in amrinone-treated dogs. Administration of saline had no effect on hemodynamic parameters. However, amrinone increased dP/dt from 1589±97 to 2077±111 mmHg/s (p<0.001) and heart rate from 139±7 to 166±9 bpm (p<0.01), but decreased LVEDP from 17±1 to 12±2 mmHg (p<0.01) and systolic pressure from 121±8 to 100±4 mmHg (p<0.025). Thus, amrinone did not increase anatomic infarct size, possibly due to its divergent effects on the determinants of myocardial oxygen demand.

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CARDIAC HYPERTROPHY AND DIASTOLIC HYPOXIC CONTRACTURE.

Beverly H. Lorell, M.D., F.A.C.C., Laura F. Wexler, M.D., Shin Momomura, M.D., Ellen S. Weinberg, Carl S. Apstein, M.D., F.A.C.C. Harvard and Boston University, Boston, MA.

A rise in left ventricular (LV) diastolic pressure occurs during angina in humans with LV hypertrophy (LVH); it is not known if the diastolic response to hypoxia or ischemia differs if LVH is present. We compared the effects of hypoxia in isovolumic (balloon-in-LV) hearts from DOC-salt hypertensive rats (LVH, n=12) with controls (C, n=13). LV/body wt differed (3.19±.36 vs 1.89±19, p<.05). Hearts were buffer-perfused at constant flow (CF) such that CF was similar in both groups (17.6±3.6 vs 20.2±5.0 [ml/min]/g LV). LV systolic pressure (LVSP, mm Hg), LVEDP (mm Hg), LV relaxation rate (T, ms), extent of relaxation (P_B,mm Hg), A-V lactate (mM/L) and coronary resistance (units.g LV) were measured at baseline (B) and at 3 min of hypoxia, (*p<.05,LVH vs C).

B	LVSP	LVEDP	T	P_B	A-V LACT	CVR
LVH	170±18*	11±1.5	20±14	3.0±4.9	.16±.15	5.8±1.7
C	103±17	10±1.0	28±7	3.6±2.7	.14±.10	6.5±2.3
Hypoxia						
LVH	66±6*	37±5.3*	44.9	33±6.7*	-.72±.23	3.7±1.2
C	38±6	22±5.0	41±10	22±4.7	-.73±.16	3.2±0.9

Thus, there was a greater rise in LVEDP with a more impaired extent of LV relaxation in LVH vs C in response to hypoxia.

Conclusion: Hypoxic diastolic contracture is exacerbated with LVH and could increase susceptibility to pulmonary congestion in patients with LVH during hypoxia or ischemia.

NORMAL VENTRICULAR DIASTOLIC FILLING IN EARLY LEFT VENTRICULAR HYPERTROPHY IN THE HYPERTENSIVE RABBIT: AN ECHOCARDIOGRAPHIC STUDY.

Jonathan Plehn, M.D., William Grice, Mary Huntington, and Carl S. Apstein, M.D., FACC. Boston University School of Medicine and Boston City Hospital, Boston, MA

The natural history of changes in diastolic function during the development of left ventricular hypertrophy (LVH) are not defined. We serially performed 2-D guided M-mode echocardiography under light sedation over 6 months in hypertensive rabbits (one clip, one kidney Goldblatt model). Systolic BP was 50% greater in the hypertensives (n=7) vs controls (C,n=7): 167±12 vs 109±9mmHg, p<0.01. Blinded echo measurements of LV mass correlated closely with the weight of the excised LV; r=0.97 for LV wt. vs M-mode LV cross-section area and r=0.94 for LV wt. vs M-mode "cubed" LV mass formula. We chose an LVH group (n=5) where all hearts had a 50% greater LV mass than the mean C value (6.8 +0.4 vs 4.5+0.1 gm, p< 0.001, LV/BW: 2.1 ±0.2 vs 1.4+1 gm/kg, p< 0.005) and, at similar heart rates, compared LV filling indices: max. posterior wall thinning rate, max. normalized LV filling rate, time to max LV filling rate. These indices were the same in the LVH and C groups (57±15 vs 52±5 mm/sec, 7.0±1.7 vs 7.4±0.4 dD/dt/D, and 60±2 vs 60±4 msec for LVH vs C respectively). Left atrial weight was increased by 53% in the LVH group.

These results show that serial echocardiographic determination of LV mass is feasible in the rabbit; this technique should facilitate studies of LVH progression and regression.

Despite a 50% increase in LV mass in our hypertensive group, LV filling indices were undiminished relative to controls, suggesting that LV filling was maintained by "compensatory" left atrial hypertrophy and increased atrial transport function.

NEUROHUMORAL RESPONSES TO PROLONGED CARDIOPULMONARY BARORECEPTOR UNLOADING IN HUMANS.

Pramod K. Mohanty, MD, FACC, Marc D. Thames, MD, FACC, James R. Sowers, MD, Carolyn McNamara, RN, Frances Beck, MS, Med. Coll. of VA, V.A. Medical Ctr., Richmond, VA.

Most studies of the reflex responses to cardiopulmonary baroreceptor unloading with lower body negative pressure (LBNP) have assessed responses during the first few minutes of LBNP. It is unknown if these early changes are representative of the steady state. Thus, we determined the responses of forearm vascular resistance (FVR) and plasma norepinephrine (NE) and renin (PRA) to prolonged (20 minutes) LBNP in 9 normal subjects. FVR, NE and PRA were measured at baseline and after 3, 10 and 20 mins of LBNP (-10, -20 and -40 mmHg). The responses to LBNP of -40mmHg are summarized in the table (*p<0.05 vs. control).

		LBNP -40mmHg		
	Baseline	3 min	10 min	20 min
Δ FVR (units)	-	53±11*	57±9*	49±12*
NE (pg/ml)	179±15	325±15*	278±20*	219±43
PRA (ng/ml/hr)	2.0±0.4	1.9±0.1	2.9±0.3	4.4±0.6*
MAP (mmHg)	87±2	87±3	90±5	88±3
HR (beats/min)	69±2	71±4	69±5	67±5

The responses to lower levels (-10 and -20mmHg) of LBNP were smaller but had a similar time course. Our data suggest that during the first 10 minutes of LBNP reflex forearm vasoconstriction is mediated solely by enhanced sympathetic activity. Renin-angiotensin system may contribute to the vasoconstrictor responses resulting only from more prolonged LBNP. These data should be taken into consideration in the design of future investigations of the neurohumoral responses to LBNP.

EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE ON VENTILATORY VARIATIONS IN ARTERIAL PRESSURE IN OPEN-CHEST PIGS. James J. Ferguson, MD, Peter Sahagian, BA, Jeanne Y. Wei, MD, FACC. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, Massachusetts

Among the profound hemodynamic effects of positive end-expiratory pressure (PEEP) is an augmentation of ventilatory variations in arterial pressure. To determine whether this phenomenon is due to direct mechanical effects of PEEP on the left ventricle, we performed experiments in 9 thiamylal anesthetized pigs. Ascending aortic pressure (micromanometer) was measured before and after a midline thoracotomy and opening the pericardium, with 0, 5, and 10 cm. of PEEP. In all cases, opening the chest and pericardium almost completely abolished baseline ventilatory variations in aortic pressure. However, with increasing amounts of PEEP, more distinct ventilatory variations in aortic pressure re-emerged.

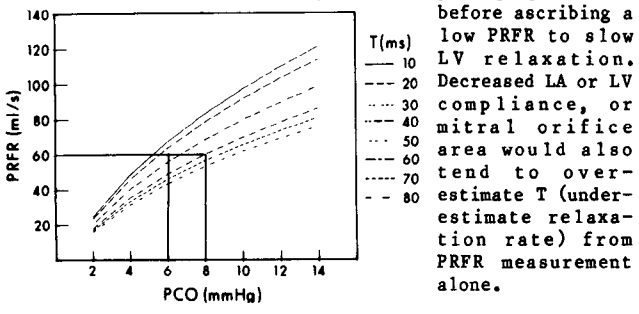
PEEP (cm)	0	5	10	
Aortic pressure variation (mmHg±SD)	2±1	5±2	8±2	* $p < 0.005$ ** $p < 0.001$

In the open chest animals, additional simultaneous pressure measurements in the pulmonary artery, left atrium, and left ventricle demonstrated similar ventilatory variations in the PA, LA, and LV pressures.

We conclude that most baseline ventilatory variation in blood pressure is abolished in an open-chest, open-pericardium preparation. However, PEEP still augments ventilatory variation in arterial pressure, even in the open-chest, open-pericardium state. This phenomenon is not due to direct mechanical effects of positive pressure ventilation on the left ventricle, but may originate from direct effects on pulmonary arterial compliance and pulmonary venous return to the left ventricle.

INFLUENCE OF LEFT ATRIAL PRESSURE AND OTHER FACTORS ON EVALUATION OF DIASTOLIC FUNCTION FROM EARLY FILLING RATE Jay S. Meisner, M.S., Yoshio Ishida, M.D., Robert W.M. Frater, M.D., F.A.C.C., and Edward L. Yellin, Ph.D. Albert Einstein College of Medicine, The Bronx, New York

Peak rapid filling rate (PRFR) is commonly used in patient studies as a noninvasive index of diastolic function because it reflects the time-constant of LV relaxation (T). However, the precise relationship between PRFR and T is unclear. Filling is also determined by other factors (e.g., LAP at mitral valve opening (PCO), LA and LV compliances, and mitral orifice area) whose individual influences are difficult to quantify. To study the problem, a computer model of LV filling dynamics was developed using data from the chronically instrumented, conscious dog. We varied T and PCO and determined PRFR for given LA and LV compliances and mitral orifice areas. The results showed that PRFR is profoundly influenced by PCO as well as T - for example, a change in PCO from 6 to 8 mmHg at a PRFR of 60 ml/s would change the predicted T from 30 to 60 ms (see Figure). Thus, one must consider an index of LAP (e.g., pulmonary capillary wedge pressure) before ascribing a low PRFR to slow LV relaxation. Decreased LA or LV compliance, or mitral orifice area would also tend to overestimate T (underestimate relaxation rate) from PRFR measurement alone.



REGULATION OF VENOUS TONE IN THYROTOXIC CALVES Richard G. Gay, MD, Christopher Appleton, MD, Richard W. Lee, MD, Gary V. Martin, MD, Marcey Olajos, BS, Eugene Morkin, MD, Steven Goldman, MD, FACC. Tucson VAMC and University of Arizona, Tucson, AZ

Hemodynamic parameters, mean circulatory filling pressure (MCFP) and blood volume (BV) were measured in 10 calves before and after 14 daily IM injections of L-thyroxine (200 ug/kg). In conscious calves, thyrotoxicosis increased ($p<.05$) heart rate (HR) by 70%, left ventricular (LV) systolic pressure (SP) by 22%, cardiac output (CO) by 120% and LV dP/dt by 56%. The MCFP, measured in anesthetized calves, during asystole induced by injection of acetylcholine (150 mg) into the pulmonary artery, increased in thyrotoxicosis from 8.3±0.7 to 11.8±0.9 mm Hg ($p<.01$). MCFP-BV curves were constructed to determine venous compliance (negative reciprocal of the slope) and unstressed vascular volume or V_u (volume intercept). Venous compliance decreased ($p<.02$) from 2.1±0.2 in euthyroid to 1.3±0.1 ml/mm Hg/kg in thyrotoxic calves. BV and V_u increased ($p<.02$) in thyrotoxicosis. When euthyroid were compared to thyrotoxic calves, both in the presence of ganglionic blockade (trimethaphan 2 mg/kg/min, N=5) or autonomic blockade (atropine .4 mg/kg and propranolol .2 mg/kg in euthyroid and .4 mg/kg in thyrotoxic calves, N=5) there were significant ($p<.05$) increases in HR from 91±8 to 136±7 and 90±2 to 149±8 beats/min, LV SP from 88±8 to 120±4 and 120±4 to 148±10 mm Hg, LV dP/dt from 1297±117 to 2215±252 and 1930±221 to 3063±504 mm Hg/sec, CO from 91±5 to 176±12 and 108±6 to 234±8 ml/min/kg and MCFP from 7.0±0.6 to 9.4±0.6 and 7.4±1.1 to 10.5±0.3 mm Hg, respectively. Thyrotoxicosis altered LV function and increased MCFP due to decreased venous compliance and increased V_u. These changes are not abolished by ganglionic or autonomic blockade and may represent direct actions of thyroid hormone.

Tuesday, March 11, 1986
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Pharmacology-Antiarrhythmic Drugs—Clinical

EFFICACY OF INTRAVENOUS AMIODARONE FOR REFRACTORY VENTRICULAR TACHYCARDIA. Richard C. Klein, MD, FACC, Charles Machell, MD, VA Medical Center, Albuquerque, NM

Antiarrhythmic efficacy of intravenous (IV) Amiodarone (Amio) was assessed in 2 patients (pt) with recurrent nonsustained (VT-NS) and 12 pt with sustained ventricular tachycardia (VT-S). VT had been refractory to at least 3 prior antiarrhythmics in all pt; 10 pt had required 1-16 DC cardioversions. Amio dosing was 5 mg/kg bolus followed by 10-15 mg/kg/24 hr infusion for 24-48 hours. VT-S was completely suppressed by Amio alone in 8/12 pt; 1 pt required addition of procainamide. 2 pt developed refractory VT/EM dissociation after 6 hrs; 1 pt had refractory VT-S after 36 hr. VT-NS was suppressed >90% in 2 pt within 30 minutes. Amio blood levels (mcg/ml) after initial bolus were:

Time(min)	5	15	30	60
Amio	8.9±1.5	6.3±2.9	2.1±1.2	1.0±0.1

Blood pressure was 118/69 prior to Amio, 110/66 after bolus ($p<0.05$), and 117/68 one hour after bolus (NS). Pulmonary wedge (PW) and cardiac output (CO) did not change except in 2 pt with ventricular dysfunction who required inotropic and balloon pump support for decreased CO due to Amio. PR, QRS, QTc intervals did not change. During follow-up oral Amio has maintained arrhythmia suppression in 6/9 pt. IV Amio as used in this dosing protocol is effective for acute therapy of refractory VT but can potentially induce severe heart failure. Long-term Amio response is not predicted by acute response consistent with different electrophysiologic mechanisms of IV and oral Amio.

THE AMIODARONE-WARFARIN INTERACTION: INCIDENCE, TIME COURSE AND CLINICAL SIGNIFICANCE.

Nicholas Kerin, M.D., F.A.C.C., Roger Blevins, Pharm.D., Lary Goldman, M.D., Kathy Faitel, B.S.N., Melvyn Rubenfire, M.D., F.A.C.C., Sinai Hospital of Detroit, and Wayne State University, Detroit, Michigan.

The amiodarone-warfarin interaction was examined in 9 patients with atrial fibrillation. Selection criteria included patients on stable doses of warfarin with at least 2 consecutive prothrombin times obtained within 2 weeks of amiodarone administration. Amiodarone was initiated in all patients with 5mg/kg infusion followed by 600-800mg/day orally for 10 days then 200-400mg/day maintenance. The prothrombin times were repeated at 1, 2, 4 weeks and 2 months after the start of amiodarone. A clinically significant change in prothrombin time was defined as a $\geq$ 15% increase within 2 months of amiodarone therapy. Seven patients (78%) had a mean 63% increase in prothrombin time (range 33-108%) which occurred during the 1st week in 5 (71%) and during the 2nd and 3rd week in 1 patient each. Among these patients the mean baseline prothrombin time was 18.6±3.5sec and the warfarin dose was 5.0±2.7mg/day. After 2 months the mean prothrombin time had returned to 20.5±4.6sec and required less warfarin in all cases (3.3±2.0mg/day, $p<.005$). We conclude that while the mechanism is unclear the amiodarone-warfarin interaction (1) is frequently seen (78%), (2) usually occurs during the 1st week, (3) is not observed after 3 weeks, and (4) results in a clinically significant reduction in warfarin requirement.

EFFECTS OF AMIODARONE THERAPY ON ACUTE POST-OPERATIVE PERIOD OF CARDIAC SURGICAL PATIENTS

M. Tuczu, M.D., J.D. Maloney, M.D., F.A.C.C., F. Sangani, M.D., K. Hocevar, R.N., L. Golding, M.D., N. Star, M.D., V. Morant, M.D., and L. Castle, M.D., F.A.C.C.
Cleveland Clinic Foundation, Cleveland, Ohio

Uncertainty exists regarding possible adverse effects of Amiodarone (A) in patients (pts) undergoing cardiac surgery (S). We compared the acute postoperative course of 20 consecutive pts on chronic A therapy for ventricular tachycardia (VT) (group 1), with 20 consecutive pts who were placed on A one or more months following similar S (group 2). A daily dosage averaging 400 mg was administered (mean of 61 days) prior to S. Factors analyzed included preoperative (demographics, A dose and duration, ventricular function), intraoperative (duration of bypass and cross-clamp), postoperative (cardiac index, systemic vascular resistance, respiratory complications, periods of intubation, ICU days, early post-op mortality.

Preoperatively severity of LV dysfunction was the only difference identifiable between group 1 & 2 (16 vs 12, statistically insignificant (SI) other than VT and A. Postoperatively group 1 more frequently had low cardiac index (3 vs 0 (SI)), low systemic vascular resistance (3 vs 1 (SI)), respiratory complications requiring prolonged intubation (4 vs 1 (SI)), early postoperative death (2 vs 0 (SI)), & day in ICU (mean 4 vs 2.2 days, statistically significant). Duration of bypass & cross clamp were similar in groups 1 and 2.

Conclusion: 1) There was a significant increase in ICU days mainly due to adult respiratory distress syndrome. Although lung toxicity was not suspected preoperatively, subclinical pulmonary toxicity of A may be the underlying cause of respiratory problem in these pts. 2) A prospective study to better define the trend of adverse influence of A on surgical pts appears indicated.

AMIODARONE FOR DRUG RESISTANT ATRIAL FIBRILLATION

Joseph A. Abbott, M.D., F.A.C.C., Mary Jane Sauve, R.N., D.N.S., Patricia Malone, R.N., M.S., Michael Eldar, M.D., Nelson Schiller, M.D., F.A.C.C., John M. Herre, M.D., F.A.C.C., Melvin M. Scheinman, M.D., F.A.C.C., University of California, San Francisco, CA.

Amiodarone (A) was instituted for treatment in 26 patients (pts) with hemodynamically unstable paroxysms of atrial fibrillation (AF) resistant to conventional therapies. Pts were followed over a mean of 20 months (range 5 to 55 months). Periodic 24-hour Holters were used to titrate A dose for control of arrhythmia. Median A dose was 200 mg (range, 200 mg week days to 1200 mg per day). Eighteen achieved constant sinus rhythm [ejection fraction (EF) 60 ± 8, LA diameter 3.9 ± .5cm] while 6 had adequate rate control during AF (EF 50 ±10 LA 4.5 ± 1 cm). Two pts failed to achieve sinus rhythm or rate control (EF 55 ± 8, LA ± 3.7 ± .5cm) Two pts had permanent pacemakers inserted for known atrioventricular (1) or sinus node (1) dysfunction prior to initiation of A dosing. No pts had adverse response to A during initial 2 weeks of loading. Fifteen pts remain on therapy; 2 died unrelated to A. Of 26 pts, 9 (35%) had side effects (7/26, 27%) or lack of control (2/26, 8%) resulting in A being discontinued; 6 pts had subsequent His bundle ablation. Late toxicity included visual disturbances (3), pulmonary fibrosis (2), ataxia (1), neuropathy (1) and hyperthyroidism (1). Conclusions: In drug resistant AF, A proved effective for most (24/26-92%), but was associated with a high cumulative incidence of toxicity despite low maintenance doses. Response to (A) could not be predicted from LV EF or LA diameter. If sinus or AV nodal dysfunction is absent, hospitalization during (A) loading may be unnecessary.

LONG-TERM EFFICACY OF AMIODARONE THERAPY IN REFRACTORY SUSTAINED VENTRICULAR TACHYCARDIA: THE ROLE OF ELECTROPHYSIOLOGIC STUDIES AND AMBULATORY MONITORING.

D Lavery, MD, S Saksena, MD, FACC, S Gordon, MD, ST Rothbart, MD, FACC, MJ Barr, RN. Newark Beth Israel Med Ctr, Newark, NJ.

We examined the value of chronic electrophysiologic studies (EPS) & followup 24hr Holter (H) monitoring in long-term management of pts with refractory sustained ventricular tachycardia (VT) treated with amiodarone (AM). 52pts, mean age 65yrs, mean LV ejection fraction (EF) 31±13%, underwent control EPS. AM (mean dose 737mg/day) was given for 4to6wks. EPS was repeated & H performed. Results of H were classified according to complexity of ventricular ectopic activity (VEA). Mean followup was 15±11 months.

RESULTS: LVEF & serum AM levels did not predict VT recurrence (Recur) on AM. All pts had spontaneous & inducible sustained VT in the drug-free state. After chronic AM therapy, the results of EPS & H were:

	EPS		HOLTER		
	Inducible VT	No Inducible VT	Complex VEA	Simple VEA	No VEA
	38 pts	14 pts	13 pts	17 pts	22 pts
VT Recur:	11(29%)	0(0%)	7(54%)	2(12%)	2(9%)
p value:	<0.03		<0.001		

3pts with inducible nonsustained VT on AM had symptomatic VT Recur after dose reduction. The sensitivity of EPS vs H monitoring for VT Recur on AM was 100% & 64%, & specificity was 39% & 85% respectively. VT Recur was most frequent in pts with inducible VT & complex VEA on H (incidence-58%; sensitivity-64%; specificity-81%). Combined EPS & H criteria improved EPS specificity but reduced sensitivity.

We conclude: 1) EPS after chronic AM Rx in pts with sustained VT is highly sensitive for clinical VT Recur; 2) Abolition of complex or all VEA during H monitoring on AM does not fully predict VT suppression; 3) Additional antiarrhythmic therapy should be considered for pts with inducible VT on AM.

AMIODARONE ALTERS SUPEROXIDE DISMUTASE ACTIVITY IN HUMAN RED BLOOD CELLS.

P. Timothy Pollak, M.D., FRCPC, Arjun D. Sharma, M.D., F.A.C.C., Rolando F. DelMaestro, M.D. FRCSC, S. George Carruthers, M.D., FRCPC, University Hospital, London.

Pathology of amiodarone pulmonary fibrosis suggests free radical induced damage. Interference by amiodarone with inactivation of free radical would be consistent with intracellular lipid inclusion bodies seen in patients (pt) on amiodarone. We examined superoxide dismutase activity (SODa) in erythrocytes (RBC) of 13 pt prior to and 1, 2 and 3 months (mo) after receiving amiodarone. Changes in SODa post amiodarone therapy formed a bimodal distribution with 2 statistically different populations based on predrug SODa ($p < 0.001$). Eight pt with a mean predrug SODa of 443.8±107.0 had an increase in SODa to 142.6%±34.6% of baseline at 1 to 2 mo and 120%±23.8% of baseline at 3 mo ($p < 0.05$). Five pt with a predrug SODa of 677.8±76.0 ng/mg-hemoglobin had a decrease to 70.9%±22.5% at 1 mo and to 65.6%±17% at 3 mo ($p < 0.05$). Thus there are differences in pt responses of SODa to amiodarone. Since drugs can both inhibit and induce the same enzyme (eg. Ethanol) the net SODa measured may include inhibition of SODa in old RBC and/or induction of SODa in new RBC. This may be the first indication that amiodarone interferes with the protection of cells from free radicals. A potential relationship between SODa responses and amiodarone pulmonary fibrosis may permit identification of patients at risk for toxicity by measuring SODa in RBC.

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Pharmacology-Antiarrhythmic Drugs—Basic

ACUTE ELECTROPHYSIOLOGIC EFFECTS AND CLINICAL LONG TERM EFFICACY OF FLECAINIDE IN PATIENTS WITH SUPRAVENTRICULAR TACHYCARDIAS

Per I.Hoff,M.D.,Bertil Øie,M.D.and Ole-Jørgen Ohm, M.D.,F.A.C.C.Medical Dept.University of Bergen,Norway

The antiarrhythmic efficacy of Flecainide acetate (FA) was evaluated during acute electrophysiologic study (EPS) and long-term treatment in 20 patients (pts);7 males,13 females,mean age 41±21 years,with paroxysmal supraventricular tachycardias (PSVT). 8 pts had dual intranodal pathways whereas 12 had accessory extranodal pathways. EPS was done before (B in table) and after intravenous FA (in table) 2mg/kg body weight (bw) over 15 min.,followed by a maintenance dose of 1.6mg/kg bw over 60 minutes. After EPS pts were treated with oral FA for 7±3 months. FA terminated PSVT by blocking retrograde fast pathway after injection of 0.9±0.5 mg/kg bw Reinduction of PSVT was prevented in 16 pts. Effects of FA on the Wenkebach point (WB) and effective refractory periods (ERP) of atrioventricular (AV) and ventriculoatrial (VA) fast pathways (FP) are shown in the table:

	AV conduction				VA conduction			
	FP ERP ms		WB beats/min		FP ERP ms		WB beats/min	
	B	FA	B	FA	B	FA	B	FA
Mean:	360	348	221	198	300	385	195	145
SD:	±76	±65	±37	±29	±50	±57	±38	±22
p-value:	NS		<0.05		<0.05		<0.05	

Long term oral treatment with FA 200-400 mg per day suppressed PSVT in 17 pts. and 400 mg was partially effective in 3 pts. Blurred vision was noted in 4 pts and in 1 pt FA was discontinued. FA is well tolerated.It is effective in the acute and long-term treatment of PSVT. This effect is mainly obtained by blocking the retrograde FP.

EFFECT OF TRIIODOTHYRONINE SUBSTITUTION DURING AMIODARONE TREATMENT FOR ARRHYTHMIAS.

R. Polikar, J.J. Goy, J. Schläpfer, Th. Lemarchand-Béraut, A. Burger, P. Magnenat, P. Nicod. Department of Medicine, Lausanne, Switzerland

Whether there is a link between the antiarrhythmic efficacy of amiodarone (A) and its blocking effect on the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) is unknown. To further assess this, we studied 7 patients (aged 32 to 62) with multiple premature ventricular contractions (PVC's) but no underlying heart disease. Each patient underwent a 48 hour Holter monitoring, an electrocardiogram and thyroid function tests including T4, T3 and reverse T3 (rT3) under no treatment (control), after 1 month of A and after a second month of A with increasing doses of T3 (up to 75 µg/day).

	T4 nmol/l	T3 nmol/l	rT3 nmol/l	PVC's/hour	qTc
Control	98	1.70	0.41	243	0.413
A	105	1.29*	0.89*	19*	0.457*
A + T3	53*	3.31*	0.56	21*	0.426

* $p < 0.05$

Treatment with A resulted in a decrease in T3, an increase in rT3, a marked diminution in PVC frequency and a prolongation of the corrected qT interval (qTc). During treatment with A + T3, T3 increased, T4 and rT3 decreased; PVC frequency remained low despite a shortening of the qTc to values not different from control. Thus: 1) T3 substitution does not abolish the antiarrhythmic efficacy of A, despite a shortening of the corrected qT interval. 2) There does not seem to be a link between the antiarrhythmic efficacy of A and its metabolic effect on the peripheral metabolism of T4.

BENEFICIAL EFFECTS OF INTRAVENOUS FLECAINIDE IN PAROXYSMAL SUPRAVENTRICULAR TACHYARRHYTHMIAS

Pierre Lacombe, M.D., Samuel Lévy, M.D., F.A.C.C., Marc Metge, M.D., Roland Cointe, M.D., Bernard Valeix, M.D., Raymond Gérard, M.D., F.A.C.C., University of Marseille, School of Medicine, Marseille, France

Previous studies on flecainide, a new class I antiarrhythmic agent, have dealt with its effect on ventricular arrhythmias. We evaluated the effect of intravenous (IV) flecainide (1.5mg/kg over 10 minutes) on paroxysmal supraventricular tachyarrhythmias with a ventricular rate (VR) >120 beats/min,in 23 patients (pts) 10 min after failure of an IV injection of a placebo (isotonic glucose). A good result, i.e. conversion to sinus rhythm (SR) or slowing of VR <100 beats/min within 10 min was obtained in 14 (61%). Seven out of 7 pts (100%) with reciprocating tachycardia found to be related to reentry within the atrioventricular node in 3 and to circus movement tachycardia involving an accessory pathway in 4, were converted to SR. Seven out of 16 pts (44%) with atrial flutter or fibrillation had a good result, including conversion to SR in 6 and slowing of VR in 1. IV flecainide was well tolerated in 20 pts. Side effects included moderate hypotension (1pt) and transient intraventricular conduction defects (2pts). This study suggests that IV flecainide is very effective for reciprocating tachycardia termination and moderately useful for the management of atrial flutter and fibrillation.

INTRAVENOUS PIRMENOL IN CONVERSION OF PAROXYSMAL ATRIAL FIBRILLATION

Lauri K.Toivonen, M.D., Markku S.Nieminen, M.D., Vesa Manninen, M.D. and M.Heikki Frick, M.D., University Central Hospital, Helsinki, Finland

Antifibrillatory effect on the atria of a new Class I antiarrhythmic agent, pirmenol, was examined in patients having atrial fibrillation of recent onset (≤48 h) and no history of sinus nodal disease and taking no antiarrhythmic drugs other than beta-blockers or digoxin. After a baseline period of 30 min a 50 mg injection of pirmenol or placebo was given double-blind in 2 min, and repeated 10 min later if fibrillation continued. Sinus rhythm was restored in 12 out of 20 patients (60%) in the pirmenol group within 2-16 min and in 3 out of 20 patients (15%) in the placebo goup within 1 hour ($p<.01$). A dose of 50 mg was effective in 7 and a total dose of 100 mg in 5 patients. In nonconverters the mean heart rate increased from 94 to 113 beats/min ($p<0.01$). A nodal rhythm at a rate of 60/min appeared for 15 s in 1 patient. Sinus arrests or atrioventricular conduction blocks did not develop. Systolic blood pressure was not changed in nonresponders or in the whole pirmenol group. The mean pirmenol plasma level was 1.3 ±0.5 (SD) mg/l 5 min after the first and 2.1 ±0.8 mg/l after the second bolus. These data indicate that pirmenol has antifibrillatory effect in the atria and suggest that pirmenol can be used intravenously in conversion of atrial fibrillation of recent onset in patients without sinus nodal disorder.

ANTIARRYTHMIC PROPERTIES OF D-SOTOLOL IN PATIENTS WITH VENTRICULAR TACHYCARDIA DETERMINED BY PROGRAMMED ELECTRICAL STIMULATION.

Joseph Schwartz, M.D., Jonathan Wynn, M.D., Sharon Maza, M.D., Barbara Laux, M.D., Deborah Keefe, M.D., Dennis Miura, M.D., John Somberg, M.D. Albert Einstein College of Medicine, Bronx, New York.

The antiarrythmic properties of D-sotolol were studied in 20 patients with cardiac arrest or symptomatic ventricular tachycardia (VT). Programmed electrical stimulation (PES) studies were performed in 14 males and 6 females, mean age 67±8 years and mean ejection fraction of 37%±5%. PES studies employed a 6 beat pacing train, cycle length of 500 msec with the introduction of 1 to 3 premature stimuli at twice diastolic threshold at the right ventricular apex or outflow tract. All patients had inducible VT by PES while off all antiarrhythmic therapy. D-sotolol was given as a 2 mg/kg dose diluted in 50 cc of D5W administered over 15 minutes. D-sotolol did not significantly change the PR, QRS or QTc intervals from baseline values. D-sotolol did significantly lower the heart rate (73 to 65 bpm) as well as prolong the ERP of the first extra stimulus (238 to 276 msec) $p<0.05$. D-sotolol did not significantly prolong the AH or HV conduction. D-sotolol prevented VT induction in 10 patients at PES, while the other 10 patients had VT provoked. All 20 patients were studied on procainamide and only 3 were protected, 2 on both drugs. Seven of the 10 patients protected by d-sotolol at PES were discharged on oral d-sotolol, dose range of 200 to 400 mg twice daily. One patient died at 1 month post discharged due to acute MI and 1 patient had a cardiac arrest, resuscitated and placed on amiodarone. The remaining 5 patients are alive and well after 5±3 months. D-sotolol appears to be an effective antiarrhythmic in selected patients and is well tolerated.

SUPPRESSION OF VENTRICULAR ARRHYTHMIAS BY RECAINAM, A POTENT NEW ANTIARRHYTHMIC.

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Recainam (R), a newly synthesized compound displaying potent class I antiarrhythmic activity, was tested in 10 hospitalized patients (pts) with frequent (>30/h) premature ventricular complexes (PVCs). Pt mean age was 57 yr (21-74); 7/10 were male; 5 had ischemic heart disease, 3 cardiomyopathy, and 2 valvular heart disease. R was given as a 3.0 mg/kg/40 min loading infusion followed by a 0.9 mg/kg/h maintenance infusion for 23 h and 20 min. Arrhythmia response was assessed both acutely (comparing 1 h post-drug loading with 2 h before) and chronically (23 h of maintenance with 48 h before). Repetitive beats were suppressed by a median of 100% both acutely ($p<0.006$) and during chronic infusion (from 80.9/h to 0/h, $p<0.003$). The median frequency of total PVCs decreased acutely by 99.6% (from 392.5/h to 1.5/h, $p<0.005$) and chronically by 99.7% (from 435/h to 1.3/h, $p<0.001$). More than 90% suppression of repetitive beats occurred in all 10 pts (100%) and of total arrhythmias in 9 pts (90%) during the maintenance period. Electrocardiographic PR and QRS intervals increased by 20% ($p<0.001$) and 25% ($p<0.003$), respectively, during therapy. However, JTc interval, an index of repolarization time, decreased by 13% ($p<0.001$). Plasma recainam concentrations averaged 5.2±0.9 μg/ml after loading and reached a steady state of 3.0±0.5 μg/ml during maintenance therapy. No adverse symptoms occurred. In summary, recainam is a promising, highly efficacious, and well-tolerated agent when administered intravenously for acute and maintenance suppression of complex ventricular arrhythmias and deserves further evaluation.

AMIODARONE – FLECAINIDE INTERACTION

Patrick Shea, MD, Kenneth Schechtman, PhD, Roop Lal, MD, Sung Soon Kim, MD, FACC, Rodolphe Ruffy, MD, FACC. The Jewish Hospital at Washington University, St Louis, Missouri.

Amiodarone(A) is commonly combined with other cardioactive drugs and is known to interact with most of them. A possible interaction between A and flecainide(F) was examined in 8 patients (mean age=58) with life-threatening ventricular(V) arrhythmias(n=7) or atrial flutter and V preexcitation(n=1). In each patient steady-state oral F preceded A, and F doses were reduced prophylactically when A was begun. Since plasma pharmacokinetics of F are nearly linear with multiple oral dosage regimens, steady-state trough flecainide plasma levels(ng/ml) were adjusted for the highest steady-state daily dose of oral F(mg) given before and during A treatment and compared. Adjusted plasma level was defined as: F plasma level/ F daily dose. The results were:

	BEFORE A	DURING A	p
I. F plasma level(mean±SD)	690±173	695±220	0.96
II. F daily dose(mean±SD)	325±103	225±113	<0.03
III.Adjusted plasma level (I/II)	2.3±0.8	3.4±0.9	<0.01

Adverse effects resulting from undesirably high plasma levels of F were effectively prevented by prophylactic reduction in F dosage. Conclusions: As with several other drugs, A interacts with F, and the concommitant use of these agents dictates a reduction in F dosage of about 1/3.

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Myocardial and Pericardial Disease

INHIBITION BY SERUM OF [^{3}H]DIHYDROALPRENOLOL BINDING TO CARDIAC β-RECEPTORS IN PATIENTS WITH HEART FAILURE

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University of Minnesota, Minneapolis, Minnesota

Cardiac β-adrenergic responsiveness is routinely decreased in patients with heart failure (HF) but the underlying mechanisms are unknown. We examined the possibility that serum factor(s) interfere with β-receptor function in 32 patients with cardiac disease (18 with idiopathic cardiomyopathy and 15 with ischemic or valvular disease); 12 normals served as controls. Cardiac dysfunction in the patients was indicated by elevated pulmonary wedge pressure (34±6 mmHg), low cardiac index (2.2±0.2 L/min) and high plasma norepinephrine NE (542±90 pg/ml). [^{3}H]Dihydroalprenolol binding to isolated cardiac myocytes was determined in vitro in the presence of serum from either controls or HF patients (1:10 to 1:400 dilution). At 1:100 dilution, sera from 15 of 18 cardiomyopathic patients were positive (26±4% inhibition of binding) compared to 7 of the 15 nonmyopathic patients (27±3% inhibition). In contrast, none of the healthy controls was positive. There was no correlation between extent of binding inhibition and plasma NE levels. Preincubation of the positive sera with antihuman γ-globulin prevented binding inhibition. These results indicate that a substantial percentage of HF patients have unidentified serum factors (? antibodies) which interact with the β-receptor binding site and may, explain the decline in β-adrenergic responsiveness.

LONG-TERM HYDRALAZINE THERAPY IN DILATED CARDIOMYOPATHY: EFFECT ON SURVIVAL.

Mazhar U. Sheikh, M.D., F.A.C.C., Ambrish K. Guipta, M.D., Fane Robinson, M.D., Robert J. Mills, M.D., F.A.C.C., Kenneth Dais, M.D., Nayab Ali, M.D., F.A.C.C., Won R. Lee, M.D., F.A.C.C., Georgetown Cardiology Section, D.C. General Hospital, Washington, D.C.

Effect of vasodilator therapy on long term survival in patients with dilated cardiomyopathy (DCM) is unknown. In this study 42 pts. with DCM were followed for an average of 68 months (M) (10-240 M). 22 pts. received digoxin and diuretics (Group I); and 20 pts. received above therapy and hydralazine (HZN) in the dose of 100-300 mg/day for a period of 19M (9-36M) (Group II). Two Groups were comparable as noted below:

	No. Pts.	Age Yrs.	Alcohol	B.P. mmHg	Mitral Regurgitation	NYH A Class III or IV
Group I	22	39.5	19	126/83	9	15
Group II	20	40.2	16	121/85	8	15

Hemodynamic data in 29 pts. prior to HZN is summarized as follows;

	No. Pts.	Heart Rate	RAP mmHg	PA mmHg	LVFP mmHg	CI
Group I	14	90	9	29.9	22.1	2.6
Group II	15	88	10.4	31.1	23.4	2.45

Result:	NYH A Class Improved at 9M	NYH A Class Worsening at 9M	Mortality at 19M	Symptoms to Death
Group I	0/22(0%)	6/22(27%)	11/22(50%)	79 months
Group II	4/20(20%)	1/20(5%)	9/20(45%)	81 months
P. Valve	0/05	N.S.	N.S.	N.S.

Conclusion: Despite the symptomatic improvement, HZN does not improve the long term survival in pts. with DCM.

THE DIRECT RELATION BETWEEN MYOCARDIAL BETA RECEPTOR DOWN REGULATION, EXERCISE INTOLERANCE, AND LEFT VENTRICULAR DYSFUNCTION IN DILATED CARDIOMYOPATHY.

Richard S. Engelmeier, M.D., John B. O'Connell, M.D., FACC, Margaret R. Eisinger, M.D., Maria Rosa Costanzo-Nordin, M.D., Patrick J. Scanlon, M.D., FACC, Loyola University Medical Center, Maywood, Illinois.

Beta adrenergic receptor density (BRD) is reduced in failing hearts explanted at transplantation. The relation of BRD to exercise capacity (METS), radionuclide left ventricular ejection fraction (EF), cardiac index (CI), and pulmonary capillary wedge (PCW) in lesser degrees of heart failure from dilated cardiomyopathy (DC) is explored by this study. Fourteen DC patients in NYHA functional class II to IV had an EF of 19.8±14%, exercise capacity of 6.8±3.8 METS, CI of 2.4±.9 L/Min/M^2, and PCW of 23±11.4 mmHg at RV endomyocardial biopsy. BRD was measured by incubating membrane preparations from 42.6±7.5mg of myocardium, with 7 dilutions of I^{125} cyanopindolol in the presence or absence of 1 uM propranolol yielding 70% specific binding. BRD averaged 19.1±9.5 femtomole/mg with a KD of 30±21 picomoles. The relation of BRD vs METS, EF, CI and PCW was analyzed by linear regression analysis as shown:

PARAMETER	METS	EF	CI	PCW
R Value	.77	.72	.50	-.60
P Value	.0010	.0036	.007	.02

Conclusion: Myocardial BRD is directly proportional to exercise capacity and EF, and inversely proportional to PCW in DC.

THE "GIANT HEART": SIGNIFICANCE OF EXTREME INCREASE IN LEFT VENTRICULAR MASS IN HYPERTROPHIC CARDIOMYOPATHY

Eric K. Louie, M.D., F.A.C.C., Barry J. Maron, M.D., F.A.C.C., NHLBI, Bethesda, Md.

Hypertrophic cardiomyopathy (HCM) is characterized by LV hypertrophy without dilatation. It is believed that greater magnitudes of LV mass may adversely affect prognosis. To study this, clinical and morphologic features in 34 patients (pts) with HCM and particularly marked LVH were analyzed. Each pt had massive septal thickening of 35-52mm; 31 (90%) also had marked free wall thickening. Despite similar morphology, clinical features exhibited a broad spectrum. Less than one-third of the pts (10) had basal LV outflow obstruction (average gradient 63mmHg); the majority (24 or 71%) showing no evidence for significant impedance to LV ejection. Although, ECG's of most pts (76%) showed LVH pattern, QRS voltages were not greatly increased (S in V_1, 27 ± 15mm; R in V_6, 21 ± 9mm), and QRS voltages were normal in 8 pts. Clinical course in 30 pts aged 14-50 years (mean 27) followed 1 year (mean 6) was variable. Dyspnea or fatigue and presyncope were the most common symptoms occurring in 67% and 60% of pts respectively. In addition, chest pain occurred in 57% of pts and syncope in 17%. No pt died, but 9 (30%) deteriorated, including 2 who spontaneously developed complete heart block and 1 who experienced ventricular fibrillation from which he was resuscitated. Most pts (21 or 70%) remained unchanged or improved. Hence, pts with HCM and "giant heart" show the most massive LV wall thickening of any cardiac disease. While this striking morphology intuitively suggests a unique clinical expression, pts demonstrated a variety of clinical manifestations and a natural history that did not reflect uniformly poor prognosis.

PERICARDIOCENTESIS GUIDED BY TWO-DIMENSIONAL CONTRAST ECHOCARDIOGRAPHY: A NEW FOOLPROOF TECHNIQUE. Martin Goldman MD FACC, Jorge Camunus MD, Jane Farhi MD, Louis Teichholz MD FACC, Bruce P. Mindich MD FACC, Mt. Sinai and St. Luke's-Roosevelt Hospitals, NY, NY

Pericardiocentesis is a potentially dangerous procedure which can be safely performed under two-dimensional echocardiographic (2DE) guidance. However, the needle tip cannot always be visualized in the ultrasound plane or an ideal ultrasound window cannot be found. Therefore, we have developed a method in which 2DE can be performed from any location to guide the pericardiocentesis. 2DE imaging is done through any convenient window while a anesthetic or saline filled syringe and long needle are inserted (preferably suxyphoid or if necessary precordially), continuously aspirating and injecting while advancing. Immediately upon entering the pericardial sac, the injected fluid creates echogenic microbubbles (contrast) confirming the needle location and the remaining fluid can be drained immediately or a catheter can be inserted.

Contrast pericardiocentesis has been performed in 10 patients with pericardial effusions of different sizes with potential technical problems ranging from tense ascites, pericardial tumors, postoperative period, pericardial adhesions and pleural effusions. The technique has been 100% successful without any complications. In all patients the contrast was immediately visible even when the needle itself was not seen. A potential limitation of this method is the identification of loculated pericardial effusions in which the injectate is not seen from the attempted imaging window. This problem is remedied by alligning the transducer along the needle path.

Therefore, pericardiocentesis performed under contrast echocardiography guidance, described here for the first time, is a safe, rapid technique which should simplify complicated pericardiocentesis and reduce the morbidity of the procedure.

Tuesday, March 11, 1986
Poster Displayed: 9:00AM–12:00NOON
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Hall D, Georgia World Congress Center
Myocardial and Pericardial Disease

LIMITED VASODILATOR RESERVE AFTER ERGONOVINE IN PATIENTS WITH DILATED CARDIOMYOPATHY AND CHEST PAIN. Richard O. Cannon, MD, FACC, Martin B. Leon, MD, FACC, Douglas R. Rosing, MD, FACC, Sebastian Palmeri, MD and Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Many dilated cardiomyopathy (DCM) pts complain of anginal-type pain despite angiographically normal coronary arteries (CA). To examine whether abnormalities of coronary blood flow exist in DCM, 20 pts with DCM (average EF=21%) and normal CA, 8 of whom had frequent chest pain (AP), underwent measurement of great cardiac vein flow (GCV-F, ml/min) and O_2 at rest and during pacing to heart rate (HR) 150. Left ventricular end-diastolic pressure (LVEDP) was measured at rest and post-pacing. During pacing alone, 5 AP pts had chest pain, associated with slightly lower GCV-F than the 15 pts without pain (122±32 vs 153±32, NS). A repeat pacing study was performed after ergonovine (E) 0.15mg iv. Data=mean±SD, BP=mean blood pressure, CR=coronary resistance (BP/GCV-F), (A-V)O_2=arterial - GCV O_2.

Rest	HR	BP	GCV-F	CR	(A-V)O2	LVEDP
No AP(12)	96±11	85±13	97±22	.95±.32	12.0±2.0	21±9
AP(8)	87±14	96±10	89±33	1.23±.47	12.4±2.2	14±7
Pacing after E						
No AP	150	95±16	163±38	.61±.14	12.3±2.5	29±5
AP	150	104±9	115±30*	.97±.26**	12.9±2.1+	24±5

*=p<0.025, **=p<0.005 vs No AP; +=<0.025 vs respective rest measurements. All 8 AP pts experienced chest pain during pacing after E despite no significant change in EKG or CA luminal diameter by angiography; no chest pain was experienced by the No AP group. Myocardial ischemia in the AP pts was suggested by widening of (A-V)O_2 difference. Thus, pts with DCM and chest pain may have dynamic limitation in coronary flow reserve, demonstrable after a vasoconstrictor stimulus. Whether this contributes to symptoms or to myocardial damage in DCM remains to be determined.

ADRENERGIC INFLUENCES ON RENAL AND CORONARY ARTERY BLOOD FLOW DURING CARDIAC TAMPONADE IN THE CONSCIOUS DOG. Gregory A. Bernath, M.D., Terrence L. Cogswell, M.D., Donna Peterson, B.S., Dennis Janzer, M.S.B.E., H. Sidney Klopfenstein, M.D., Ph.D., Medical College of Wisconsin and Zablocki VA Medical Center, Milwaukee, Wi.

We examined the role that adrenergic mechanisms play in controlling renal and coronary blood flow during progressive cardiac tamponade (CT). Six chronically instrumented, unanesthetized, conscious dogs were studied. Cardiac output (electromagnetic flowprobe), intrapericardial pressure, aortic and right atrial blood pressures, and renal (RABQ) and coronary (CABQ) artery blood flows were recorded (Doppler flowprobes). Forty-five episodes of CT were induced by intrapericardial pressure saline infusion during control (no blockade), alpha blockade (phenoxybenzamine), or beta blockade (propranolol) from baseline (empty pericardium) to decompensation (decline in blood pressure to 70% of baseline).

Blood Flow (% of Baseline) at Decompensation

	Control	Alpha Blockade	Beta Blockade
CO	34.82 *	58.14 *	47.85 *
RABQ	74.15 #	89.9	99.23 #
CABQ	34.76 *	94.5	56.85 *

= p < .05 compared to others in column.
* = p < .05 compared to its baseline flow.

Thus RABQ is much better preserved than CO, independent of adrenergic mechanisms. Furthermore, coronary artery blood flow in the absence of alpha adrenergic blockade decreases to approximately the same degree as cardiac output, suggesting that adjustments in CABQ during CT are primarily dependent on alpha adrenergic mechanisms.

MYOCARDIAL PERFUSION ABNORMALITIES IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY AND NORMAL CORONARY ARTERIES. Patrick T. O'Gara, MD, Robert O. Bonow, MD, FACC, Barbara A. Damske, RN, Barry J. Maron, MD, FACC, Paolo Spirito, MD, Stephen L. Bacharach, PhD, Michael B. Green, MS, Steven M. Larson, MD, and Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Chest pain is a prominent symptom among pts with hypertrophic cardiomyopathy (HCM) even in the absence of large vessel coronary artery disease (CAD). Evidence indicates that this pain, as well as many features of the natural history of HCM, derives from an ischemic origin. We used Thallium-201 (Tl-201) single photon emission computed tomography and planar scintigraphy to evaluate myocardial perfusion in 18 pts with HCM immediately after symptom-limited treadmill exercise and at rest after a 3 hr delay. None had associated CAD, but 12 pts had a history of angina. Resting LV ejection fraction (EF) ranged from 0.30 to 0.99 (mean=0.58±0.27). Reversible regional perfusion defects were identified in 9 of the 18 pts: 7/9 had a history of chest pain, although exercise-induced chest pain did not predict reversible abnormalities. Irreversible perfusion defects occurred in 6 of the 18 pts: 5/6 had resting LVEF ≤0.47. In 3 of these 5 pts serial echocardiographic data were available and demonstrated progressive LV wall thinning and/or cavity dilatation over 3-11 years; the other 2 had large apical aneurysms with corresponding Tl-201 defects. Thus, 1) reversible regional perfusion defects, suggestive of ischemia, and 2) fixed defects, suggestive of myocardial scar and associated with reduced LVEF, frequently occur in HCM pts. These results suggest that myocardial ischemia not only contributes to symptoms in HCM, but may also result in fibrosis and transmural scar, and thereby to LV dysfunction, in a sub-

VALUE AND LIMITATIONS OF ECHOCARDIOGRAPHY IN DETERMINING THE CAUSE OF CONGESTIVE CARDIOMYOPATHY.

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To differentiate ischemic from idiopathic congestive cardiomyopathy (CCMP) 56 patients (pts), all with cineangiographic LV ejection fraction of ≤31%, were studied by two dimensional echocardiography. Coronary artery disease was present in 30 pts. Wall motion was evaluated in 8 RV and 13 LV segments, each graded on a 6 point scale from -1 (hyperkinesis) to +4 (aneurysmal). Wall motion score (WMS) of RV and LV was the sum of the scores for each segment.

	idiopathic CCMP (n=26)		ischemic CCMP (n=30)
LV-WMS	17.1±3.8 (12-26)	n.s.	18.1±3.4 (12-24)
RV-WMS	6.5±2.0 (3-10)	*	3.7±1.5 (1- 7)
LV/RV WMS	2.9±1.0 (1.4-5.5)	*	5.8±2.4 (2.8-12)

* - p<0.01

Coronary artery disease was absent in 16/17 pts with a LV/RV WMS ratio of <3.0 and present in 19/21 with a ratio of >4.3. Segmental hyperkinesis of LV was only seen in ischemic CCMP (8/3 = 27%). LV aneurysm (well demarcated bulge in LV contour during both diastole and systole) was seen in 12 pts of whom 9 (75%) had ischemic CCMP. All 10/26 (38%) idiopathic CCMP pts with left bundle branch block had an early systolic downward septal dip on M-Mode, whereas this was consistently absent in the 13/30 (43%) ischemic pts. Thus: 1) A LV to RV WMS ratio of <3.0 and >4.3 is highly associated with an idiopathic respectively ischemic CCMP; 2) LV segmental hyperkinesis is only seen in ischemic CCMP; 3) LV aneurysm is highly associated with ischemic CCMP; 4) Early systolic downward septal dip on M-mode is only seen in pts with left bundle branch block and idiopathic CCMP.

REVERSIBLE LEFT VENTRICULAR DIASTOLIC ASYNCHRONY AND REGIONAL VARIATION IN MAGNITUDE OF EARLY DIASTOLIC FILLING IN HYPERTROPHIC CARDIOMYOPATHY.

Robert O. Bonow, MD, FACC, Dino F. Vitale, MD, Stephen L. Bacharach, PhD, Terri M. Frederick, RN, Barry J. Maron, MD, FACC and Michael V. Green, MS, NHLBI, Bethesda, Md.

Left ventricular (LV) relaxation and diastolic filling are impaired in many pts with hypertrophic cardiomyopathy (HCM). To investigate the influence of regional heterogeneity on these global abnormalities, we studied 48 HCM pts by radionuclide angiography at rest. All were in sinus rhythm with a diastasis interval evident in each LV time activity curve. LV regional function was assessed by subdividing the LV region of interest into 20 sectors from which regional time activity curves were derived. Regional variation in timing between minimum volume and peak filling rate (ΔTPFR) was used as a measure of diastolic asynchrony, and the inter-sector difference in percent contribution of rapid filling to end-diastolic volume (EDV) was used to measure regional variation in the magnitude of rapid LV filling (ΔRFP). Pts with HCM had greater ΔTPFR (35±24 vs 12±6 ms, p<.001) and greater ΔRFP (17±8 vs 8±3 %, p<.001) than 30 normal subjects, indicating asynchronous and heterogeneous diastolic function. Studies were repeated in all pts after 1-2 wks of oral verapamil, which decreased both ΔTPFR (to 21±16 ms, p<.001) and ΔRFP (to 13±7%, p<.02). These regional changes were related to improved global diastolic filling: rapid filling increased in both rate (3.3±1.1 to 4.4±1.1 EDV/sec, p<.001) and magnitude (69±15 to 85±15 % of LV stroke volume, p<.001). Thus, more uniform regional diastolic performance after verapamil was associated with enhanced global LV filling. These findings indicate that asynchronous and nonuniform regional diastolic function may contribute importantly to the severity of impaired LV diastolic filling in HCM.

SUPERIORITY OF CARDIAC DIMENSIONAL CHANGES COMPARED TO STANDARD HEMODYNAMIC INDICES FOR THE DETECTION OF HUMAN ALLOGRAFT REJECTION

David E. Hansen, M.D., George T. Daughters, M.S., Edwin L. Alderman, M.D., F.A.C.C., Neil B. Ingels, Ph.D., Edward B. Stinson, M.D., F.A.C.C., D. Craig Miller, M.D., F.A.C.C., John C. Baldwin, M.D., Philip E. Oyer, M.D., Ph.D., F.A.C.C., Geraldine C. Derby, R.N., Stanford University, Stanford, CA.

Although hemodynamic abnormalities have been well described in human allograft rejection, their measurement by non-invasive techniques has not proved sufficient for early detection, necessitating serial myocardial biopsies. We compared hemodynamic and ejection phase indices with precise measurements of cardiac dimensions provided by computer-aided analysis of fluoroscopy of 9 intramyocardial markers implanted in the anterior, inferior, and lateral LV walls and aortic valve margins. Measurements of the velocity of circumferential fiber shortening (VCF), end-diastolic volume (EDV), and end-systolic volume (ESV) were obtained. Hemodynamic measurements, fluoroscopic marker recordings, and RV myocardial biopsies were carried out prospectively in 7 heart transplant recipients, starting 6 days postoperatively.

Nine episodes of acute allograft rejection with myocyte necrosis occurred. Comparision of pre-rejection measurements with those obtained during rejection showed no significant change in heart rate, cardiac output, pulmonary capillary wedge pressure, mean arterial pressure, isovolumetric relaxation time (by echo), ejection fraction, or VCF. However, EDV increased significantly from 168±39 to 200±50 ml (p<.002) and ESV increased from 108±37 to 131±48 (p<.007). We conclude that precise measurements of alterations in dimension may more readily detect early rejection than standard hemodynamic indices.

SYMPATHETIC NERVOUS SYSTEM ACTIVITY IS RELATED TO LEFT VENTRICULAR DIASTOLIC FILLING IN DIABETES MELLITUS.

Joel K. Kahn, M.D., Benjamin Zola, M.D., Jack E. Juni, M.D., Aaron I. Vinik, M.D. University of Michigan, Ann Arbor, Michigan.

The etiology of impaired left ventricular diastolic filling in patients with diabetes mellitus is unknown. We measured indices of diastolic filling by analysis of high temporal resolution radionuclide time-activity curves in 28 normotensive long-term diabetics without evidence of ischemic heart disease by clinical and stress thallium scintigraphic exams. Six (21%) diabetics had abnormal diastolic filling and differed from diabetics with normal filling only in their greater severity of cardiac autonomic neuropathy (CAN) measured by non-invasive maneuvers (p<.05) and lower norepinephrine levels in the supine (131.1±24.7 vs. 356.2±58.4 pg/ml, p<.01) and the upright (224.9±47.8 vs. 673.3±122.3 pg/ml, p<.005) positions. The diabetics with CAN (n=15) had depressed diastolic filling compared to their non-neuropathic counterparts measured as time to peak filling rate (154.2±12.0 vs. 119.1±10.6 msec,p<.05) and time to peak filling rate normalized to the cardiac cycle length (24.3 ±2.2 vs. 16.2±1.5 %,p<.01). Of the various tests of autonomic nervous activity, the fall in systolic blood pressure with standing, a reflex arc involving mainly sympathetic pathways, correlated strongest with impaired diastolic filling (p<.001). Age, duration of diabetes, and the degree of microvascular complications did not correlate with any of the indices of diastolic filling. Thus, in patients with diabetes mellitus alterations in sympathetic nervous system activity are important correlates of altered left ventricular diastolic filling.

SUPERIOR SENSITIVITY OF THE VOLTAGE-MASS RELATIONSHIP FOR THE NONINVASIVE DIAGNOSIS OF CARDIAC AMYLOIDOSIS.
Michael Simons MD, Jeffrey Isner MD, FACC, Natesa Pandian MD, Marvin Konstam MD, FACC. Tufts-New England Medical Center, Boston, Massachusetts.

Previous studies have indicated that cardiac amyloidosis (A) results in a relatively unique combination of ECG and echocardiographic (E) findings: diminished QRS voltage (calculated as the sum of V1R+V5R) associated with increased cardiac mass (calculated as LV cross-sectional area using 2DE). The present study was designed to evaluate the sensitivity of this relationship in comparison with 2 other previously described noninvasive findings in cardiac A: a "sparkling" (S) appearance of the myocardium on 2DE; and myocardial uptake of technetium-99m-pyrophosphate (TcPYP). In 13 pts (Group I), the diagnosis of cardiac A was established by endomyocardial biopsy, necropsy and/or restrictive/constrictive physiology associated with extra-cardiac tissue biopsy-proven A. In Group I, sensitivity of 2DE-S was 44%; sensitivity of TcPYP was 50%. In 7 additional pts (Group II), the clinical diagnosis of cardiac A was made on the basis of cardiac symptomatology associated with extra-cardiac tissue-proven A. In Group II, sensitivity of 2DE-S was 40%; sensitivity of TxPYP was 42%. In contrast, the plot of the voltage-mass relationship for Group I (mean voltage/mass ratio = 0.77±0.37; range = 0.1 to 1.55) and Group II (mean voltage/mass ratio = 0.85±0.29 (range = 0.45 to 1.21) pts clearly separated them from normal controls with only one exception (sensitivity = 92%), a pt with long-standing systemic hypertension. Evaluation of specificity was not possible in this study due to absence of necropsy, biopsy, or hemodynamic "gold standard" in pts with systemic A but no apparent cardiac A. Conclusion: the sensitivity of the voltage/mass relationship derived from combined analysis of ECG and 2DE is superior to 2DE-S and TcPYP for the noninvasive diagnosis of cardiac A.

ATRIAL FAILURE IN CARDIAC AMYLOIDOSIS.
Jonathan F. Plehn, M.D., Martha Skinner, M.D., Alan S. Cohen, M.D. and Carl S. Apstein, M.D., F.A.C.C. Boston City Hospital and Boston University School of Medicine, Boston, MA.

Clinical congestive heart failure due to impaired LV filling (diastolic failure) with normal or near-normal systolic function is common in patients with an increased LV mass due to amyloid infiltration or myocardial hypertrophy. We hypothesized that these two conditions might differ in regard to the atrial contribution to LV filling.

We compared the Doppler trans-mitral flow patterns in 4 patients with biopsy-proven primary systemic amyloidosis and cardiac amyloid infiltration to 4 patients with myocardial hypertrophy (LVH) due to hypertension or primary hypertrophic cardiomyopathy. The patients were matched for similar LV mass as assessed by LV cross-sectional area (amyloid: 28.9±4.2cm^2 vs. LVH: 29.3±6.3cm^2).

The amyloid patients had a marked reduction of atrial function compared to the LVH group as assessed by peak atrial trans-mitrial flow velocity (A) relative to peak early diastolic trans-mitral velocity (E); the A/E ratios were, LVH: 1.57±0.31; Amyloid: 0.50±0.17, (mean±SEM, n=4/group, $P<.025$).

Conclusion: Atrial failure is an important component of the diastolic failure observed in cardiac amyloidosis and may be characteristic of this condition.

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Author Present: 9:00AM–10:00AM
Hall D, Georgia World Congress Center
Electrophysiology—Basic

THE CARDIAC POTENTIAL FIELD CREATED BY CHEST WALL DEFIBRILLATION ELECTRODES IN DOGS

Peng-Sheng Chen, M.D., Patrick Wolf, B.S.E.E., Frank J. Claydon, M.S., Ellen G. Dixon, M.S., Nitaro Shibata, M.D., William M. Smith, Ph.D., and Raymond E. Ideker, M.D., Ph.D. Duke University Medical Center, Durham, North Carolina

Although transthoracic ventricular defibrillation (DF) has been used clinically for many years, there has been no direct measurement of the cardiac potential field created by chest wall electrodes. Accordingly, in 5 dogs with the chest opened through a median sternotomy, 60 epicardial and 36 anterior RV intramural plunge electrodes were applied to the heart. The halves of the sternum were then reapproximated, and saline-soaked gauze was interpositioned to fill the gap. Unipolar potentials were recorded while 5 volt shocks were given through 78 cm^2 electrodes applied to the right and left chest wall at the midaxillary lines. Potential gradients tangential to the epicardium and along the plunges were calculated. The voltage drop from the right to the left margins of the heart was only 6±4% of the total voltage applied. The potential gradient tangential to the epicardium varied widely over the surface of the ventricles. The mean ratio of the highest to the lowest tangential epicardial gradient was 36.9±27.1. The ratio of the endocardial-epicardial gradient along the plunge to the tangential epicardial gradient near the insertion of the plunge was 2.6±5.2. Thus for right and left chest wall DFs, most of the applied voltage is dissipated outside the heart, and the tangential epicardial potential gradient is uneven. These results indicate the tremendous inefficiency of DF with chest wall electrodes and raise the possibility that much better locations and sizes of DF electrodes can be found by measuring the potential field.

INFLUENCE OF PATHWAY LOCALIZATION ON EFFECTIVE REFRACTORY PERIODS OF ACCESSORY ATRIOVENTRICULAR PATHWAYS

Michael Kentsch, M.D., Klaus-Peter Kunze, M.D., Karl-Heinz Kuck, M.D., Walter Bleifeld, M.D., F.A.C.C., Dept. of Cardiology, University Hospital Eppendorf, Hamburg, West Germany

In 44 patients (pts) (14 women, 30 men; mean age 39 years) with an accessory AV pathway (AP) undergoing standard electrophysiologic study the relations between the effective refractory periods (ERPs) of myocardial tissue and ERP of the AP were studied and the dependence of the ERP of AP on AP location were analyzed. We determined ERPs of RA, LA via coronary sinus, and RV with the extrastimulus technique, of AP in anterograde (ant) direction during decremental atrial pacing at the site of atrial AP insertion, and of AP in retrograde (ret) direction during decremental RV pacing. If ERP of AP was shorter than ERP of the stimulated myocardial tissue (MT) ERP of AP was estimated to be 10 msec less than ERP of MT. Ant ERP of AP did not differ from ret ERP of AP in right sided APs. In left sided APs ant and ret ERP of AP was not different from ERP of LA. In right sided, APs, ant ERP of AP differed significantly from ERP of RA (282 ± 46 ms vs 224 ± 43 ms, $p < .01$) and from ERP of RV (217 ± 10 ms, $p < .01$). No significant difference was found between ret ERP of AP and ERP of RA and RV. There were no linear correlation s between ant ERP of right-sided APs and ERP of RA ($r = .53$), and ant ERP of left-sided APs and ERP of LA ($r = .42$). Multivariate analysis of ERP depending on AP localization showed significant differences between ant ERPs of right septally located and left laterally located APs (311 ± 48 ms vs 248 ± 24 ms; $p < .05$), but no differences in ERPs of right lateral (255 ± 10 ms), left posterior septal (269 ± 34 ms) and left posterior free wall (257 ± 27 ms) APs. Moreover, there was a linear decrease of ant ERP from right septal to left lateral APs. — Conclusions: 1. Ant and ret ERP of AP do not correlate with ERP of myocardial tissue. 2. Ant ERP of AP decreases significantly from right septal to left lateral APs. A significant linear decrease of ant ERP of AP was shown from right septal to left lateral AP.

SUBEPICARDIAL ORIGIN OF SPONTANEOUS ECTOPIC BEATS IN THE INFARCTED DOG HEART.

Eugene Patterson, Ph.D., Benjamin J. Scherlag, Ph.D., FACC, and Ralph Lazzara, M.D., FACC. Univ of Oklahoma Health Sciences Center and VAMC, Oklahoma City, OK.

Endocardial (ENDO) and epicardial (EPI) recordings were used to determine the earliest activation site for spontaneous ventricular beats, 24 hr after coronary artery ligation. In 13 experiments, premature ventricular beats (PVBs) and slow ventricular tachycardia with a left bundle branch block morphology and a Δ-wave in the anterior EKG leads were observed. EPI activation overlying the central infarct zone preceded ENDO activation by 20-80 msec. Early EPI activation was simultaneous with the Δ-wave of the EKG. In any individual experiment, EPI activation was coupled to the previous beat by a constant, fixed interval. In no experiment was epicardial or endocardial electrical activity recorded during this interval. The mean coupling was prolonged by lidocaine from 385±24 to 409±45 msec ($p<0.01$), and was decreased by epinephrine (364±7 msec) and D-600 (324±32 msec) ($p<0.05$). Histologic examination of the EPI site revealed surviving tissue sparsely connected to surrounding myocardium by narrow tissue (<1 mm) bands through infarcted tissue. Lidocaine pledgets or intracoronary latex were used to ablate spontaneous PVBs of EPI origin without altering ENDO PVBs. The observations suggest an EPI origin for some PVBs after infarction. The PVBs may result from electrotonic excitation of EPI tissue from the ischemically-injured zone with slow active conduction from the site of origin to the remaining ventricular tissue.

ELECTROPHYSIOLOGIC EFFECTS OF HIGH K^+ AND RAPID STIMULATION ON AUTOMATICITY OF THE RABBIT SINOATRIAL NODE.

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Electrophysiologic mechanisms underlying the suppression of automaticity by high K^+ and after rapid stimulation were studied using small rabbit sinoatrial (SA) nodal preparations (0.2 x 0.2 x 0.1 mm). When extracellular K^+ concentration was increased from 4 to 8 mM, the spontaneous firing frequency was decreased from 226 to 186/min, accompanied by reductions in the maximal diastolic potential from -72 to -62 mV, take-off potential from -48 to -38 mV and rate of diastolic depolarization from 94 to 71 mV/sec ($P<0.01$, n=6). SA nodal recovery time after stimulation at 375/min for 30 sec was 230 msec during control, and was prolonged to 512 msec at 8 mM K^+ ($P<0.01$, n=5). Voltage clamp experiments revealed that 8 mM K^+ did not affect the slow inward current, but decreased the outward K^+ current (i_K) tail from 30 to 26 nA and increased the hyperpolarization-activated inward current from 9 to 12 nA ($P<0.01$, n=5). Deactivation time constant of the i_K tail was increased from 135 to 160 msec at -60 mV and its steady-state activation curve was shifted to more negative potentials by 4 mV by high K^+. After 10 rapid depolarizing pulses at a rate of 375/min, the deactivation time constant of the i_K tail was increased to 210 msec in 4 mM K^+ and to 240 msec in 8 mM K^+ ($P<0.01$, n=5). These results suggest that high K^+ and rapid stimulation suppress the SA nodal automaticity by inhibiting the deactivating process of the i_K tail. Possible extracellular K^+ accumulation by the rapid stimulation was also suggested.

EFFECT OF TRANSMURAL VERSUS NONTRANSMURAL MYOCARDIAL INFARCTION ON INDUCIBILITY OF VENTRICULAR ARRHYTHMIAS DURING STELLATE STIMULATION

John M. Herre, M.D., F.A.C.C., Yuh-Lin Lin, M.D., A. Scott Mills, M.D., Lewis Wetstein, M.D., F.A.C.C., and Marc D. Thames, M.D., F.A.C.C., Medical College of Virginia, Richmond, VA.

Transmural myocardial infarction (MI) interrupts sympathetic nerves and denervates viable muscle distal to MI. In order to determine the importance of this denervation, we measured ventricular effective refractory period (VERP) and ease of inducibility of ventricular tachycardia (VT) or fibrillation (VF) by programmed stimulation from the right ventricle (RV) and left ventricle (LV) in 16 dogs before and during left stellate stimulation (LSS). Transmural MI was produced in 6 dogs by latex injection into the left anterior descending (LAD). Nontransmural MI was produced in 6 dogs by LAD ligation. Dogs were studied ≥14 days after MI. Four dogs with no MI served as controls. Denervation of LV distal to transmural MI was demonstrated by absence of fall in VERP with LSS.

Results:	Δ VERP with LSS (msec, mean±SEM)		Increased Ease of Inducibility with LSS	
	RV	LV	RV	LV
Control	-16±4	-15±4	0/4	1/4
Transmural MI	-11±2	- 1±1	6/6	3/6
Nontransmural MI	-12±3	-11±4	1/6	0/6

We conclude that 1) in normal hearts and in hearts with chronic nontransmural MI, LSS produces balanced changes in VERP and no increased inducibility and 2) in hearts with partial denervation produced by transmural MI, LSS produces unbalanced changes in VERP and increased ease of inducibility of VT or VF.

CORRELATES OF VENTRICULAR FIBRILLATION DURING MYOCARDIAL ISCHEMIA SUPERIMPOSED ON EARLY AND LATE MYOCARDIAL INFARCTION IN A CANINE MODEL

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Thirty dogs underwent apical myocardial infarction (MI) created by the ligation of the mid left anterior descending coronary (LAD) artery and all visible collaterals. Acute, reversible myocardial ischemia was superimposed one day after MI (Early) in 15 dogs and 2 weeks after MI (Late) in the other 15. Reversible ischemia was created by alternate 10-minute occlusions of proximal LAD or proximal first left circumflex marginal artery (LCxM). Each occlusion was repeated to test the reproducibility of the arrhythmias. Myocardial blood flow before and 2 minutes after the onset of ischemia was measured by microsphere technique in 6 Early and 6 Late dogs. The incidence of reproducible, ischemia-related ventricular fibrillation is shown:

	LAD occlusion		LCxM occlusion
Early (1 day)	8/15	$p<0.02$	6/15 NS
Late (2 weeks)	1/15		9/15

The incidence of ventricular fibrillation did not correlate with MI size (21±6% in Early and 22±7% in Late). Ischemia-related ventricular fibrillation was invariably preceded by reduction of myocardial flow to at least 15% of control in a critical mass of myocardium regardless of the coronary vessel occluded and did not occur when flow reduction was less severe. Thus, spontaneous ventricular fibrillation in the setting of ischemia following MI is a blood flow-related phenomenon. The differences in the incidence of ventricular fibrillation between early and late LAD occlusion, and between late LAD and late LCxM occlusion are associated with the differences in the severity of reduction in myocardial perfusion.

MYOCARDIAL ISCHEMIA SUPERIMPOSED ON LATE MYOCARDIAL INFARCTION: A CANINE MODEL OF ISCHEMIA-RELATED VENTRICULAR ARRHYTHMIAS

Hasan Garan, M.D., Jeremy N. Ruskin, M.D., F.A.C.C., Massachusetts General Hospital, Boston, MA

Post-myocardial infarction ventricular arrhythmias associated with superimposed myocardial ischemia or induced by programmed ventricular stimulation (PVS) were investigated in 15 dogs, two weeks following the ligation of the left anterior descending coronary artery (LAD). All animals underwent PVS from RV and LV, before and after episodes of acute, reversible myocardial ischemia created by 10-minute occlusions of the proximal first circumflex marginal artery superimposed on 2-week old anteroapical infarction. Myocardial blood flow, before and 2 minutes after the onset of ischemia, was measured by microsphere technique in 6 animals. The incidence of sustained ventricular tachycardia (SUSVT) and ventricular fibrillation (VF) are shown.

	Ischemia-induced	PVS-induced
SUSVT	0/15	5/15
VF	9/15	8/15

The response to baseline PVS was reproducible following the reversal of ischemia in 14/15 animals. PVS-induced SUSVT, in the absence of ischemia, correlated with MI size by logistic regression analysis. Ischemia-induced VF, however, correlated not with MI size, but with the total size of the myocardium with critically reduced (<15% control) blood flow during the ischemic episodes. Thus in this model of late myocardial infarction SUSVT does not appear to be an acute ischemia-related arrhythmia. The incidence and the underlying substrates of PVS-induced and acute ischemia-induced ventricular arrhythmias may be different.

VERAPAMIL-INDUCED SUSTAINED VENTRICULAR TACHYCARDIA IN ISOLATED, PERFUSED RABBIT HEARTS. A UNIQUE EXPERIMENTAL MODEL FOR IDIOPATHIC VENTRICULAR TACHYCARDIA.

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Inducibility and characteristics of sustained paroxysmal ventricular tachycardia (SPVT) were studied in 12 isolated perfused rabbit hearts. Induction of SPVT was attempted by rapid electrical stimulation (5 msec square pulses at 20-25 Hz for 2-5 sec) applied at RV outflow tract or LV apex. SPVT was not induced under normal perfusing conditions, whereas SPVT was produced in all 12 hearts after verapamil (0.5-1 mg/L) was added to the perfusate. Epicardial activation was mapped with either a roving electrode or 18 close bipolar surface electrodes. QRS patterns during the SPVT either remained stable for a prolonged period or showed occasional transition to different morphologies, but never showed torsade de pointes configuration. The rate of SPVT ranged from 460 to 800/min. Excluding 5 hearts in which observations were discontinued after >60 min, the SPVT lasted from 24 to 268 min (mean 120 min). The earliest epicardial activation site was located in LV in 5, RV in 5 and near the anterior interventricular groove in 2. Excitation appeared to spread radially from these sites in 11, whereas a large circus movement was suggested in one. Overdrive pacing for 15-30 beats in 6 hearts captured the ventricles but failed to terminate SPVT. Addition of disopyramide (5 mg/L) resulted in termination of SPVT in 3 out of 7, whereas washout of verapamil terminated it in 4 out of 5 hearts. In one heart, exploration of LV cavity with a roving electrode abruptly terminated SPVT. Although neither abnormal automaticity nor micro-reentries can readily explain its mechanism, this arrhythmia serves as a unique experimental model for the so-called idiopathic ventricular tachycardia. Possible clinical implications of these findings are stressed.

CYCLIC AMP PROLONGS QT INTERVAL BY AN ACTION ANTAGONISED BY ADENOSINE IN THE RAT HEART.

Wilhelm F. Lubbe, MD, FACC, Andrew Gilchrist, B.Sc. and Robyn Holland, Department of Medicine, University of Auckland and Green Lane Hospital, Auckland, New Zealand.

In the isolated rat heart adenosine opposes cyclic AMP induced lowering of the ventricular fibrillation threshold and antagonises spontaneous arrhythmias after coronary artery ligation. The influence of dibutyryl cyclic AMP (DBcAMP) on QT interval was assessed by measurement of QT/RR ratio on 100mm/sec recordings of ECG in Langendorff perfused rat hearts. DBcAMP, infused at 5.0umol/min (290-310nmol/ml) increased heart rate from 270±7 to 310±14bpm; despite this, QT/RR increased from 0.39±0.09 to 0.65±0.4 ($p<0.001$). Adenosine, 50umol/l in perfusate during DBcAMP infusion, reduced QT/RR to 0.52±0.3 ($p<0.001$). Analogs of adenosine were used to determine its site of action. 2-Chloroadenosine, which is not transported into the cell, did not reduce QT/RR when slowing of heart rate was prevented. In contrast, erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), 10umol/l, which inhibits adenosine deaminase and increases tissue adenosine levels threefold, reduced QT/RR to 0.24±0.2 ($p<0.001$) without alteration in heart rate. N^6-phenylisopropyladenosine (PIA) and 5'-N-ethylcarboxamidoadenosine (NECA), agonists for extracellular R sites, did not alter QT/RR when reduction of heart rate was prevented by ventricular pacing.
Cyclic AMP and adenosine have opposite effects on vulnerability to fibrillation and on QT interval in the rat heart; the potent action whereby EHNA shortens QT interval and lack of effect of analogs acting at extracellular sites favor an intracellular site of action (P site). These observations suggest that cyclic AMP and adenosine are determinants of the QT interval.

CATHETER MEDIATED ELECTRICAL ABLATION: THE RELATION BETWEEN CURRENT AND PULSE WIDTH ON VOLTAGE BREAKDOWN AND SHOCK-WAVE GENERATION.

Gust H Bardy,MD,FACC, Fernando Coltorti,MD, Michael Rackson,BSEE, Karl Hanson,BSEE, H Leon Greene,MD,FACC, Tom D Ivey,MD. Univ WA, Seattle, WA.

A limitation of catheter mediated electrical ablation of cardiac tissue is shock-wave induced barotrauma. Electrically, shock-wave formation is characterized by a breakdown in the voltage waveform.

Our purpose was to study how current amplitude and pulse width(PW) relate to voltage breakdown at the time of shock-wave generation using constant current, rectangular pulses delivered from a high-voltage, variable waveform modulator with a wide dynamic range and bandwidth. A 6Fr 16mm^2 surface area Cu electrode immersed in bovine blood was the cathode and an 8.5cm disc electrode was the anode. Waveforms were monitored oscilloscopically and delivered energy was determined by integrating the voltage and current waveforms. For any given current, voltage breakdown and shock-wave generation occurred at substantially different PW's. The PW recorded is the maximum duration possible for a particular current before voltage breakdown occurs. Voltage and energy prior to breakdown are shown below.

Current(Amps)	2	4	6	8	10	12	14	16
PW(μsec)	2500	780	320	180	140	96	72	62
Voltage (Volts)	160	320	470	650	760	930	1130	1200
Energy(Joules)	0.8	1.0	0.9	0.9	1.1	1.1	1.1	1.2

Conclusions: A "strength-duration" curve can be constructed which defines the limits of PW for any given current in order to avoid voltage breakdown associated with shock-wave generation. The total energy deliverable in a single pulse without incurring this phenomenon is relatively small. Very short duration, high amplitude pulses allow for higher voltages and energies before shock-wave generation occurs.

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GALLOPAMIL (METHOXY-VERAPAMIL) INDUCES TRIGGERED ACTIVITY IN CARDIAC CELLS

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It has been observed that intravenous verapamil may elicit transient, multiform ventricular tachycardia in patients, by an unknown mechanism. To test for the possible arrhythmogenic effects of verapamil, guinea pig ventricular fibers were studied in vitro and stimulated at a cycle length of 500 msec. Tissues were superfused with a 5.6mM K^+ Tyrodes solution for 1 hr and with 2.0-mM K^+ for an additional 2-3 hrs. Action potentials (AP) were recorded by standard techniques. In 2.0-mM K^+ maximum diastolic potentials (MDP) of Purkinje fibers hyperpolarized from -81±1 mV to -94±2 mV and remained stable. Gallopamil (G) (1 μM) caused an increase in early repolarization, but terminal repolarization was delayed leading to early afterdepolarizations (EAD) and also triggered APs 4 min after G. Triggered APs were coupled to stimulated APs by an average of 170 msec and showed the same MDP (-94 mV), $\dot{V}_{max}$ (430 V/s) and overshoot (+40 mV). Some of the triggered APs were followed by EADs. Both triggered APs and EADs disappeared in 25 min after G was given. We conclude that G-induced triggered APs and EADs at low $[K^+]_o$ may be the counterpart of the polymorphous arrhythmias seen in patients, after verapamil. The delay of terminal repolarization may indicate a reduction in repolarizing K-current. G, a known inhibitor of slow inward current decreases Ca^{++} influx during the plateau of the AP, and secondarily may lead to partial inactivation of repolarizing currents and generation of EADs and triggered APs.

INHIBITION IN ISOLATED HUMAN MYOCARDIUM

John R. Windle, M.D., Douglas P. Zipes, M.D., F.A.C.C., Eric N. Prystowsky, M.D., F.A.C.C., Robert F. Gilmour, Jr., Ph.D., F.A.C.C. Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN

Previous studies demonstrated that a stimulus (S_c) delivered within the ventricular effective refractory period (ERP) inhibited a subsequent suprathreshold intensity stimulus (S_2) from producing a propagated response (inhibition). The purpose of this study was to demonstrate inhibition in human ventricular trabeculae (n=10) obtained at heart transplantation and to determine the effects of S_c current intensity, S_c pulse duration, S_1S_c interval, and hyperkalemia on prolongation of action potential duration and change in ERP (ΔERP) produced by S_c. Action potentials were recorded at sites near (<2mm) and remote (1-2cm) from a bipolar stimulating electrode during superfusion with normal or hyperkalemic (KCL = 8 - 12mM) Tyrode. The ERP was the longest S_1S_2 interval that failed to produce a propagated action potential. S_c was delivered within the ERP and the ΔERP determined. Results: 1) S_c increased action potential duration and ERP by producing local responses, 2) ΔERP increased with increasing S_c current intensity (5-10mA), pulse duration (10-30ms), or S_1S_c interval (130-250ms) 3) hyperkalemia enhanced the increase in ΔERP by S_c, 4) during hyperkalemia S_c delivered to the near recording site prevented S_2 delivered to the remote site from producing a propagated response. Thus, S_c increased ERP by producing nonpropagated local responses; this effect was enhanced by hyperkalemia. S_c-induced local responses in vivo might produce conduction block and cause or prevent reentrant excitation.

Tuesday, March 11, 1986
4:00PM–5:30PM, Room #313/314
Doppler Echocardiographic Assessments of Aortic Valve Disease

ASSESSMENT OF THE SEVERITY OF AORTIC REGURGITATION BY PULSED DOPPLER ABDOMINAL AORTIC FLOW PATTERN

Katsu Takenaka, MD, Ali Dabestani, MD, Julius M Gardin, MD, FACC, Daniel Russell, Sandra Clark, Alice Allfie, Walter L Henry, MD, FACC.
University of California, Irvine, California

Doppler echocardiography is a useful noninvasive method for detecting aortic regurgitation (AR). However, Doppler methods for quantification of AR either involve relatively time-consuming procedures or are affected by associated valvular diseases such as aortic or mitral stenosis. To determine if the presence of retrograde holo-diastolic flow in the abdominal aorta (ABD Ao) can be used to assess the severity of AR, we examined flow in ABD Ao by pulsed Doppler echocardiography in 15 normal subjects, 10 patients without AR and 31 patients with AR confirmed by aortography. In 31 patients with AR, 12 had mitral regurgitation, 11 had mitral stenosis, 8 had aortic stenosis, 5 had mitral prosthetic valves and 5 had aortic prosthetic valves. No retrograde diastolic flow was found in ABD Ao of 15 normal subjects and 10 patients without AR. Twenty of 21 patients with 1+ or 2+ AR independently determined by injection of iodinated contrast into the aortic root did not have retrograde holo-diastolic flow in ABD Ao while all of 10 patients with 3+ or 4+ AR had retrograde holo-diastolic flow in ABD Ao. In one patient with 1+ AR and a left-to-right shunt through a patent ductus arteriosus, retrograde holo-diastolic flow was detected in ABD Ao.
In conclusion, the finding of holo-diastolic retrograde flow in abdominal aorta is useful in distinguishing patients with severe AR from those with mild or absent AR. Moreover, the method is easy to perform and appears to be independent of the presence of other cardiac diseases except patent ductus arteriosus with significant left-to-right shunt.

DIRECTION AND WIDTH OF AORTIC REGURGITANT JETS: ASSESSMENT BY DOPPLER COLOR FLOW MAPPING.

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University of Washington, Seattle, WA

To study the direction and width of aortic regurgitant jets, we evaluated 14 patients (pts) with aortic regurgitation (AR) by Doppler color flow mapping (using an IREX 880 instrument). Pt ages ranged from 50-80 (mean 62) years, with 8 men and 6 women. AR etiologies: calcific=6; rheumatic=5; degenerative, congenital, root disease=1 each. We measured AR direction in both long-axis and 4-chamber planes, with reference to the direction of the left ventricular outflow tract (LVOT). Jets directed < ± 20^0 from the LVOT centerline in both planes were considered "parallel"; jets with greater angulation to the LVOT were considered "oblique". Jet width, measured 1cm below the aortic valve, was normalized for diastolic LVOT diameter at this level and classified as broad (filling >70% of the LVOT), moderate (35-70% of the LVOT), or narrow (<35% of the LVOT).

In all pts, discrete diastolic AR jets were visualized in the LVOT. Of 11 pts with 1-2+ AR, jet width was narrow in 6, moderate in 4, and broad in only 1. Of the 3 pts with 3-4+ AR, jets were broad (n=2) or moderate (n=1); no pt with significant AR had a narrow jet. Jets were parallel to the LVOT in 8 pts (2 with significant AR), and oblique in 6 (only 1 with significant AR).

We conclude that diastolic jets of AR show substantial variability, in both width and direction, from pt to pt. Since broad jets generally denoted significant AR while narrow jets were never severe, the width of an AR jet may be a clue to severity. Finally, the oblique orientation and narrow profile of many jets may make it difficult to record their velocity accurately throughout diastole; this may explain why LV filling pressure cannot be measured successfully from AR velocity in some pts.

COMBINED COLOR DOPPLER AND CONTINUOUS WAVE DOPPLER IN THE EVALUATION OF AORTIC STENOSIS

Frederick Helmcke, M.D., Gilbert J. Perry, M.D., Navin C. Nanda, M.D., F.A.C.C., University of Alabama, Birmingham, AL

We compared peak to peak and mean catheterization (cath) gradients with peak instantaneous and mean continuous wave Doppler (CW) gradients (using the Bernoulli equation) in 2 groups of patients: Group A-12 patients in whom the stenotic jet (SJ) was visualized by color Doppler (CD); Group B-24 patients evaluated by CW alone (SJ not visualized by CD in 12 patients, CD not performed in 12 patients). CW correlated better with angiography when the SJ could be seen by CD reflecting optimal alignment of the CW beam with the direction of the SJ, which was often eccentric.

	CW instantaneous vs cath peak-peak	CW mean vs cath mean
Group A	r=.91, p<.001	r=.93, p<.001
Group B	r=.76, p<.001	r=.86, p<.001

The CD width of the SJ at its origin (from R parasternal and/or suprasternal view in 10 patients, L parasternal long axis view in 2 patients) provided an independent estimate of the severity of aortic stenosis; 4/4 patients with SJ width <.8cm had a mean cath gradient >50mm, while 8/8 patients with SJ width>.8cm had a mean cath gradient <50mm. We conclude: 1) CD facilitates optimal alignment of the CW beam with the SJ resulting in improved correlation with cath gradients; 2) CD allows the measurement of the width of the SJ, which independently confirms the severity of aortic stenosis; 3) CD is limited by the fact that the SJ was visualized in only 12/24 (50%) patients.

DO ASYMPTOMATIC PATIENTS WITH AORTIC STENOSIS REQUIRE VALVE REPLACEMENT SURGERY?

Thomas A. Kelly MD, Mark L. Smucker MD, FACC, Robert M. Rothbart MD, Robert S. Gibson MD. University of Virginia, Charlottesville, Virginia

With the advent of continuous-wave Doppler(CWD), more pts with asymptomatic (ASx) aortic stenosis (AS) are now being identified. Since natural history data are scant and retrospective, we prospectively followed 90 consecutive pts(age 67±17) with CWD≥50mmHg(range 50-134) for 1-39 mos. Previous work by our group in 72 additional symptomatic (Sx) AS pts(age 65±8) verified the accuracy of CWD vs cath (r=.92,p<.0001). All 90 pts were followed until death or valve replacement(AVR) and serial CWD was performed. At entry, 51 were ASx and 39 were Sx. The groups were similar with regard to: CWD gradient(68±19vs68±17); murmur grade (3.2vs3.1); ↓A2 or carotid upstroke(61vs66%);LVH(86vs92%); and subsequent AVR(10vs15%). Sx pts were older(63vs72yrs,p =.01), had lower LVEF(63vs53,p<.001), had more ECG strain (48vs76%,p=.01) and ↑LA size(63vs84%,p=.02). When all entry 2D echos were computer analyzed, Sx pts had greater end-diastolic(ED) wall thickness(28vs24mm,p<.001), ED myocardial area(60vs49 cm^2,p=.001) and derived LV mass(522vs 404g,p=.002). At 15±8 mos follow-up, 16 ASx pts(31%) became Sx and 18 Sx pts(46%) progressed. Follow-up CWD demonstrated higher gradients in the initially ASx pts who became Sx vs those who remained ASx(ΔCWD:23±5vs2±3 mmHg,p=.001). Only 1 ASx pt(2%) suffered cardiac death; this was nonsudden, after CHF onset. There were 14 cardiac deaths in the Sx group(36%,p<.001); 5 were sudden(p=.01). Thus, in contrast to Sx pts, ASx pts with significant AS by CWD and clinical criteria: 1)have a good prognosis at 15mos and are at minimal risk for cardiac death; 2)serial CWD may help identify ASx pts who are prone to symptoms; 3)ASx pts are less likely to exhibit ECG strain and have lower LV mass which may be related to their more favorable outcome; and 4)AVR can be deferred until symptoms develop.

ACCURATE NONINVASIVE ASSESSMENT OF AORTIC REGURGITATION UTILIZING A DOPPLER HALFTIME INDEX

Steve M. Teague, MD, James A. Heinsimer, MD, Jerome L. Anderson, MD, Edwin G. Olson, MD, and Udho Thadani, MD, FACC, University of Oklahoma Health Sciences Center and VA Hospitals, Oklahoma City and Durham, NC.

We utilized continuous wave Doppler ultrasound to quantitate aortic regurgitation utilizing a velocity halftime method analogous to the Doppler approach to mitral stenosis. Sixty four patients with chronic aortic regurgitation underwent catheterization to determine angiographic grade (Angio) and aortic valve diastolic pressure halftime (AVgrad). Six patients with acute, severe regurgitation underwent valve replacement on the basis of clinical and echocardiographic findings alone. Doppler halftime (DHT) was the time required for the high velocity subvalvular diastolic profile to decay by 30%. DHT and AVgrad (means ± std. dev.) are compared to Angio grades:

Number	23	24	12	11
Angio	1+	2+	3+	4+
DHT	.64±.14*	.46±.09*	.26±.07*	.18±.08
AVgrad	.61±.13*	.48±.10*	.28±.06*	.19±.07

DHT correlated with AVgrad (corr coef .91) and Angio (.83), but not with left ventricular end diastolic pressure (-.59), pulse pressure (-.35), or ejection fraction (.32). DHT seperated all but 3+ and 4+ Angio grades (*p<.003), and identified 6 of 6 patients with severe regurgitation requiring urgent valve replacement (DHT <.15). Doppler aortic regurgitation velocity halftime has clinical utility and estimates hemodynamic and angiographic severity.

COLOR DOPPLER ASSESSMENT OF AORTIC INSUFFICIENCY IN TWO ORTHOGONAL PLANES

Gilbert J. Perry, M.D., Frederick Helmcke, M.D., Navin C. Nanda, M.D., F.A.C.C., University of Alabama, Birmingham.

We previously showed that regurgitant jet (J) width (W)/LV outflow tract width (JW/LVOW) measured by color Doppler in the parasternal long axis view correlates with aortic angiography (AA), while length and long axis area do not. In an attempt to improve accuracy, we compared long axis JW/LVOW with J area (A)/LVO area (LVOA) in the parasternal short axis view, both measured by computerized planimetry immediately beneath the aortic valve. J was seen in long axis in 31/31 and in short axis in 25/31 patients (PTS). Long axis JW/LVOW correctly predicted AA grade in 26/31 PTS (84%); 5/31 (16%) were misclassified by 1 grade (table). Short axis JA/LVOA correctly predicted AA in 24/25 PTS (96%); 1/25 (4%) was incorrectly classified by 1 grade.

Angiograms	Short Axis JA/LVOA	# PTS	Long Axis JW/LVOW	# PTS
Grade I	< 3%	4/5	1-24%	6/7
	5%	1/5	25-49%	1/7
Grade II	4-25%	4/4	1-24%	2/7
			25-49%	5/7
Grade III	26-60%	6/6	50-67%	5/6
			68%	1/6
Grade IV-V	>60%	10/10	53%	1/11
			>67%	10/11

We conclude that J size relative to LVO size just beneath the aortic valve correlates well with AA grade. Short axis JA/LVOA correlates better with AA than long axis JW/LVOW, probably because the short axis view visualizes the jet in 2 dimensions; however short axis JA/LVOA was available in only 25/31 PTS (81%).

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #264/265/266
Nuclear Cardiology: New Imaging Strategies

CARDIAC IMAGING AND MYOCARDIAL KINETICS OF TECHNETIUM-TERTIARY BUTYL-ISONITRILE DURING DIPYRIDAMOLE INDUCED HYPEREMIA Robert Okada, Steven Williams, Charles Boucher, Kenneth McKusick, Donna Dragotakes, Jean Garneau. Saint Francis of Tulsa Medical Research Foundation, Mass. Gen. Hosp. and New Engl. Nucl., Tulsa OK and Boston MA.

Technetium-tertiary butyl-isonitrile (Tc-TBI) has been shown in our laboratory to produce gamma camera images of excellent quality in resting dog models of coronary stenosis. However, Tc-TBI will most likely be used in conjunction with exercise or dipyridamole vasodilation. Accordingly, 14 dogs had partial occlusion of the left anterior descending coronary artery (LAD) such that reactive hyperemia was partially to completely attenuated. Dipyridamole was then infused IV over 4 minutes creating hyperemic flows in the left circumflex (LCX) coronary system. 5 mCi of Tc-TBI was then administered IV. LAD and LCX zone regionaly myocardial Tc-TBI activities were continuously monitored using miniature implantable radiation detectors and gamma camera imaging over 4 hours. The electrocardiogram, blood pressure, distal coronary artery pressure, sonomicrometer determined regional myocardial wall thickness, and cardiac output were also monitored. Microsphere determined regional myocardial blood flows demonstrated an LAD/LCX flow ratio of .45 +/- .25 (SD) during dipyridamole. Despite this difference in flow, Tc clearance rates were minimal and equal in the LAD and LCX zones (4 hr. fractional clearance = .16 +/- .12 for LAD and .17 +/- .11 for LCX, p=ns). Gamma camera images were of excellent quality and demonstrated the LAD defect in all dogs. In conclusion: 1) Tc-TBI injected during dipyridamole induced hyperemia produces excellent gamma camera images. 2) There is minimal washout and no redistribution into the initial defect over time, and thus image quality is stable over time. 3) These findings and the 140 keV gamma make Tc-TBI a promising new cardiac perfusion imaging agent.

NON-IMAGING NUCLEAR PROBE MEASUREMENT OF LEFT VENTRICULAR VOLUME DURING RAPIDLY CHANGING LOADING CONDITIONS: VALIDATION USING SONOMICROMETER-DETERMINED VOLUMES IN CONSCIOUS DOGS. Peter F. Lord, D.V.M., Forrester A. Lee, M.D., Michael Simons, M.D., Wallace Byrd, Harvey J. Berger, M.D., F.A.C.C., Barry L. Zaret, M.D., F.A.C.C. Yale School of Medicine, New Haven, CT.

The nuclear probe is used frequently to assess LV function during changing hemodynamic conditions. Few data are available concerning the accuracy of this technique under loading conditions which grossly alter LV volume and geometry.

Studies were performed on four conscious dogs instrumented with ultrasonic crystal pairs surgically implanted along short and long axes of the LV. Nuclear probe measures of end diastolic (ED), end systolic (ES) volume, stroke volume (SV) and EF were compared to sonomicrometer data in 73 matched gated (4-15) beats digitized at 100 Hz. LV volume was changed rapidly by occlusion of the vena cava, pulmonary artery, and/or aorta with or without concurrent infusion of isoproteronol, propranolol, nitroprusside, or atropine. Probe volumes were calibrated against sonomicrometer volumes by setting background counts to a fixed fraction of ED counts at the beginning of each study. Background was subsequently adjusted only for decay. Heart rate varied from 41-207 bpm, EDV from 16-143 ml, and ESV from 7-111 ml. Excellent correlations were obtained between sonomicrometer and probe data:

	EDV	ESV	SV	EF
slope	0.84	0.84	0.81	0.96
r	0.97	0.98	0.81	0.81

Thus, the nuclear probe can accurately track rapidly changing LV performance under varying loading conditions which alter LV volume and geometry.

I-123 PHENYLPENTADECANOIC ACID: ALTERATIONS IN MYOCARDIAL DISTRIBUTION FOLLOWING EXERCISE IN CONCENTRIC LEFT VENTRICULAR HYPERTROPHY. Christopher L. Wolfe, M.D., James R. Corbett, M.D., Padamakar V. Kulkarni, Ph.D., Patrick L. Kennedy, M.D., Donald E. Jansen, M.D., and James T. Willerson, M.D., F.A.C.C., Univ of Texas Health Sci Ctr, Dallas, TX.

Regional alterations in myocardial substrate uptake and/or utilization have been demonstrated in hypertensive rats. To determine if alterations in left ventricular (LV) fatty acid uptake and/or utilization might be present in patients (pts) with LV concentric hypertrophy (LVH), we compared rest and exercise I-123 phenylpentadecanoic acid (IPPA) myocardial scintigraphy in 10 hypertensive pts and 15 normal (NL) volunteers. All LVH pts had normal coronary arteries by angiography and concentric LVH by 2-D echocardiography. Quantitative segmental analysis demonstrated heterogeneous LV IPPA activity in LVH pts compared to NLS following exercise (23±8% vs 13±5% difference in mean maximal segmental activity at 4 minutes, $p<0.01$). Exercise thallium-201 (Tl-201) scintigraphy was normal in 6 of the 7 LVH pts tested. In LVH pts there was a significantly greater variation in mean maximal segmental activity of IPPA as compared to Tl-201 (25±5% vs 16±6%, $p=0.013$). The LV distribution of IPPA at rest was similar in LVH patients and NLS. IPPA washout rates in LVH pts were uniform and similar to NLS at rest and following exercise. We conclude that: (1) compared to NLS, pts with LVH demonstrated heterogeneous myocardial IPPA activity following exercise but not at rest; (2) LV washout of IPPA was uniform in LVH pts and similar to NLS; (3) the distribution of IPPA following exercise in LVH pts is more heterogeneous than that of Tl-201; (4) pts with LVH may have altered myocardial uptake and/or utilization of fatty acids following exercise.

NONINVASIVE IMAGING OF CARDIAC ALLOGRAFT REJECTION USING INDIUM-111 MONOCLONAL ANTIMYOSIN. Linda J. Addonizio, M.D., Robert E. Michler, M.D., Charles Marboe, M.D., Peter E. Esser, PhD, Lynne L. Johnson, M.D., F.A.C.C., David W. Seldin, M.D., Eric A. Rose, M.D., Welton M. Gersony, M.D., F.A.C.C., Paul J. Cannon, M.D., F.A.C.C., Columbia University, New York, NY.

The acute rejection of cardiac allografts is currently diagnosed by the presence of myocyte necrosis on endomyocardial biopsy. Indium-111 labeled monoclonal antimyosin Fab (In-111mAM) binds to disrupted myocytes and has been used to image myocardial infarction. To test whether allograft rejection can also be detected and quantified scintigraphically, 6 dogs that had undergone intrathoracic heterotopic cardiac allograft transplantation were injected with In-111mAM while in various stages of acute rejection. Planar and single photon emission tomographic (SPECT) images were obtained 24 hours later. Four dogs had allografts older than 8 months and had been on chronic immunosuppression; 2 dogs had allografts less than 2 weeks and were not immunosuppressed. Ratios of activity (CR) comparing heterotopic to native hearts were calculated from both SPECT images and in vitro scans of excised and sectioned hearts, then rejection was scored histopathologically. In-111mAM uptake was not visible in planar or SPECT images of native hearts. Faint diffuse uptake was apparent in cardiac allografts on chronic immunosuppression and intense radioactivity was present in hearts with ECG evidence of rejection. The heterotopic to native heart CR in the excised hearts with rejection correlated well with both CR in SPECT images ($r=0.93$, range 1.7-7.7, mean 4.7±2.9) and histopathological rejection score ($r=0.97$). We conclude that imaging with In-111mAM provides a noninvasive method to detect the presence, location, and severity of cardiac allograft rejection.

MEASUREMENT OF PERCENTAGE MYOCARDIUM INFARCTED USING SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY, THALLIUM-201 AND INDIUM-111 MONOCLONAL ANTIMYOSIN FAB

Andrew M. Keller, M.D., Lynne L. Johnson, M.D., F.A.C.C., Kenneth S. Lerrick, M.D., Jonathan N. Zimmerman, M.D., James Coromilas, M.D., F.A.C.C., David W. Seldin, M.D., Peter E. Esser, PhD, Paul J. Cannon, M.D., F.A.C.C., Columbia University, New York.

Infarct size (IS) expressed as percentage myocardium infarcted (PMI) is clinically more useful than IS expressed as absolute mass. We tested the hypothesis that PMI can be measured non-invasively in vivo using single photon emission computed tomography (SPECT) dual isotope imaging in a dog model. Nine dogs were subjected to balloon catheter coronary artery occlusion followed by injection with Indium-111 monoclonal antimyosin Fab (In-111 mAM). After Indium imaging 24 hours later, Thallium-201 (Tl-201) was injected and the animals reimaged. Animals were then sacrificed, their hearts excised, weighed, and true IS measured using triphenyl tetrazolium chloride. IS in grams was estimated from normalized reconstructed Indium SPECT images, and non-infarcted myocardium (NIM) in grams was estimated from obliquely reconstructed Thallium SPECT images. A 75% threshold iso-contour boundary was used for edge detection. Estimated PMI was calculated by dividing estimated IS by the sum of both estimated IS plus estimated NIM. True PMI was calculated by dividing true IS by true myocardial weight. Linear regression analysis yielded the following relationship: Estimated PMI = 1.04 X True PMI + 5.4 percent ($r = 0.84$, $p<.01$, standard error of the estimate = 9.6 percent). True PMI ranged from 9.7 to 46.2 percent (mean 22.9 $\pm$ 13.2 standard deviations). We conclude that dual isotope SPECT with In-111 mAM and Tl-201 can accurately estimate PMI.

CAN IN VIVO QUANTITATIVE PLATELET SCINTIGRAPHY PREDICT IN VITRO PLATELET DEPOSITION WITHIN INTRAARTERIAL THROMBI: VALIDATION OF SINGLE AND DUAL RADIOISOTOPIC TECHNIQUES.

Jules Y. T. Lam, M.D., James H. Chesebro, M.D., F.A.C.C., Mrinal K. Dewanjee, Ph.D., Juan J. Badimon, Ph.D., and Valentin Fuster, M.D., F.A.C.C., Mayo Clinic, Rochester, MN.

^{111}In-labeled platelet (0.3-0.5 mCi) scintigraphy alone or in combination with ^{99m}Tc-labeled red blood cell (2 mCi) subtraction scintigraphy appears promising for detecting platelet-thrombus formation, but the reliability of their quantitative indices is uncertain. We have thus validated the single and simultaneous dual isotope scintigraphic technique for quantitating platelet deposition within the thrombus formed during angioplasty (5 inflations to 6 ATM, 30 seconds each, 1 min apart) of the common carotid arteries in 12 normal pigs. The ^{111}In-excess ratio (IE), an in vivo quantitative index of platelet deposition (PD) derived from dual isotope scintigraphy, as well as two reported indices derived from single isotope scintigraphy, the thrombus to blood ratio of ^{111}In (TBR) and the ^{111}In counts/100 pixel/μCi of ^{111}In injected (CPP) were correlated with the absolute PD (platelets x $10^6/cm^2$) determined in vitro. There was a strong exponential correlation between IE and in vitro PD ($r=0.81$, $p<0.001$) and a fair correlation between both the TBR or CPP and in vitro PD ($r=0.63$ $p<0.03$, and $r=0.64$ $p<0.02$, respectively). The standard error of the estimate was 1.8, 2.2, and 2.2 platelets x $10^6/cm^2$ for IE, CPP, and TBR respectively. Thus, both single and dual scintigraphic techniques can be used to reliably quantitate the in vivo acute platelet-thrombus formation following angioplasty, but since the correlation and standard error of the estimate appears to be better by dual isotope scintigraphy, it may be more reliable when tested simultaneously in a larger population.

Tuesday, March 11, 1986
4:00PM–5:30PM, Room #264/265/266
Signal Averaging and Other New Techniques for Arrhythmia Analysis

ABNORMALITIES IN THE SIGNAL AVERAGED ELECTROCARDIOGRAM IN PATIENTS WITH VENTRICULAR TACHYCARDIA AND LEFT BUNDLE BRANCH BLOCK

K. Elizabeth Kindwall, MD, Roxellen Auletto, RN, Rita Falcone, MS, Michael B. Simson, MD, FACC, Univ. of PA, Phila., PA

Low amplitude, high frequency signals late in the QRS complex correlate with the presence of ventricular tachycardia (VT) in patients after myocardial infarction (MI). Patients with left bundle branch block (LBBB) had been excluded from prior studies. We examined a population of 37 patients with LBBB using signal averaging and 25 Hz high pass bidirectional filtering. Twenty-four had inducible sustained VT, and thirteen had no ventricular arrhythmia. Twenty-four had prior MI; the others had nonischemic, dilated cardiomyopathy.

Results:	QRS Duration (msec)	Amplitude (μV) Last 40 msec of Filtered QRS
LBBB VT	177+26	20.9+10.4
LBBB No VT	160+18	39.6+19.6

The high frequency content in the early and midportions of the QRS were similar in VT and no VT groups. The QRS duration was longer in the VT group ($p<.05$). The LBBB-VT group had a lower amplitude in the last 40 msec of the filtered QRS than the LBBB-no VT group ($p<.001$). A value of <30 μV in the late QRS complex predicted VT in the LBBB patients with a sensitivity of 79%, a specificity of 61%, and a positive predictive accuracy of 79%. Among patients with MI, those with VT had a lower amplitude in the last 40 msec of the filtered QRS than those without VT (22.2+11 vs 37.5+18.5 μV, $p<.05$). VT patients without MI also had a lower amplitude in the last 40 msec of the QRS (17.4+71.0 vs 46.0+19.9 μV, $p<.01$). We conclude: Patients with LBBB and VT have characteristic abnormalities in high frequency content late in the QRS which distinguish them from LBBB patients without VT.

THE SIGNAL-AVERAGED ECG PREDICTS RESULTS OF PROGRAMMED STIMULATION IN PATIENTS WITH NONSUSTAINED VENTRICULAR TACHYCARDIA AFTER INFERIOR INFARCTION

Alfred E. Buxton, M.D., FACC, Michael B. Simson, M.D., FACC, Rita A. Falcone, M.S., Francis E. Marchlinski, M.D., FACC, Mark E. Josephson, M.D., FACC Univ of PA, Philadelphia, PA

We performed programmed stimulation and signal-averaged ECGs in 36 consecutive patients (pts) with nonsustained ventricular tachycardia (VT-NS) following inferior (27) or anterior (9) myocardial infarction. Sustained (S) VT was induced in 19 pts. Pts with inferior infarction and inducible VT-S had longer filtered (>25 Hz) QRS (132+19 vs 110+14 ms, $p<.01$), and lower voltage in the last 40 ms of the filtered QRS (16+9 vs 29+14 μV, $p<.01$), than pts without inducible VT-S. Pts with anterior infarction and inducible VT-S had shorter filtered QRS than pts without inducible VT-S (95+10 vs 115+10 ms, $p<.02$), but no significant difference in the amplitude of the last 40 ms of the QRS (73+4 vs 34+35 μV, p=NS). We defined an abnormal signal-averaged ECG as filtered QRS duration >110 ms and amplitude of <25 μV in the last 40 ms of the filtered QRS. Applying these criteria to identify pts with inferior infarction having inducible VT-S results in:

	Abnormal QRS duration	Late potential
Sensitivity	1.00	.80
Specificity	.58	.33
Predictive Value	.75	.60

We conclude: 1) for pts with inferior infarction and spontaneous VT-NS, the signal-averaged ECG provides a sensitive tool for prediction of inducible VT-S. 2) In pts with VT-NS after anterior infarction, the signal-averaged ECG is not helpful in predicting inducibility of VT-S.

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SIGNAL AVERAGING OF HIGH GAIN HOLTER EKG RECORDINGS - VALIDATION OF A NEW TECHNIQUE FOR DETECTION OF AFTER-POTENTIALS.

George J. Kelen, M.D., Raphael Henkin, M.S., Mark Restivo, M.S., Robert H. Zeiler, Ph.D., Edward B. Caref, B.S., Nabil El-Sherif, M.D., F.A.C.C., SUNY, Downstate and VA Medical Centers, Brooklyn, New York.

Signal averaging techniques have been widely used to demonstrate low amplitude after-potentials in the ST segment as well as HIS bundle activity on a surface EKG. To our knowledge, there has been no previous report of averaging successfully performed on 24 hour Holter tapes. A separate belt-worn module was designed to pre-amplify (gain X100) and filter (40-200Hz) the surface EKG signal presented to one channel of a conventional two channel Holter recorder. During playback at both real time and 120X real time, the signals were passed to a custom designed trigger circuit driving the same 12 bit signal averager we use for real-time recordings and averages accumulated over 100 to 800 beats. In six patients with after-potentials and six with easily visible HIS activity on convential real-time signal-averaging, the averaged signals derived from Holter tapes correlated closely in timing, appearance and noise level. This new technique appears to have several advantages:- 1) Clean low noise signals for extended periods whilst the patients is asleep. 2) Multiple patients can be taped simultaneously on separate recorders and the averaging done at a later time. 3) The time required to accumulate averages of large numbers of beats is greatly reduced by rapid playback of the tape. It remains to be seen whether after-potentials demonstrated on Holter recordings differ in clinical significance from those detected on conventional random recordings.

LOW FREQUENCY REQUIREMENTS FOR REPRODUCTION OF ISCHEMIC ST SEGMENT ABNORMALITIES DURING ACTIVITY IN MAN.

Greg A. Imperi, MD, Charles R. Lambert, MD PhD, and Carl J. Pepine, MD, FACC, VAMC and University of Florida, Gainesville.

Evaluation of patients with silent or symptomatic myocardial ischemia often involves ambulatory electrocardiographic (ECG) monitoring. Although several investigators have stressed the need for FM monitors with low frequency response extending to DC (0 Hz) for reliable reproduction of ischemic ST segment abnormalities, data to support these reccomendations are lacking. The objective of the present investigation was to determine whether extended low frequency response is needed for reproduction of ischemic ST segment abnormalities. Bipolar ECG recordings were made from 5 men with coronary artery disease before, during, and after erect bicycle exercise using a high fidelity instrumentation amplifier and FM tape recorder. All patients had ischemic ST segment abnormalities during exercise while 3 patients experienced angina and the remaining 2 remained asymptomatic throughout the test. Using a radix 2 fast Fourier transform algorithm (FFT) and a variable sampling rate into a 1024 place input array, FFT spectra were calculated with low frequency content extending to either 0.20, 0.98, or 1.95 Hz for both resting and exercise ECGs. From these spectra ECG tracings were resynthesized using the inverse FFT and compared to the original records. Visual inspection of the original and resynthesized ECG tracings revealed no obvious differences whether low frequency content extended to 0.20, 0.98, or 1.95 Hz. Numerical comparisons were made by calculating the coefficient of determination (R^2) between the original and resynthesized ECG's. R^2 (mean±SD) for these comparisons was 0.998±0.001. In conclusion the amplitude response characteristics of ECG recording equipment does not require an extended low frequency range such as that found in FM systems to accurately reproduce ischemic ST segment abnormalities induced by activity in man.

ACCURACY OF DETECTION OF MYOCARDIAL ISCHEMIA BY AMPLITUDE-MODULATED AND FREQUENCY-MODULATED HOLTER TECHNIQUES.

Thomas L. Shook, MD, C. William Balke, MD, Peter W. Kotilainen, Andrew P. Selwyn, MD, FACC, Peter H. Stone, MD, FACC. Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Use of amplitude-modulated (AM) ambulatory ECG (AECG) to detect myocardial ischemia has been limited by concern that inadequate low-frequency response or phase shift may cause inaccurate or artifactual ST segment recordings. To determine the acccuracy of AM and frequency-modulated (FM) AECG systems, we recorded the signal from the same set of two bipolar chest leads simultaneously by standard ECG, and AM and FM AECG recorders in 14 patients during treadmill exercise (ETT) and by simultaneous AM and FM recorders in 9 patients during ambulatory outpatient activities (16 sessions).

From the ETT recordings, ST deviation, R- and S-wave amplitude, and RR-interval were measured in 543 ECG complexes. The AM system accurately reproduced ST segments as recorded by standard ECG (range 5.0 mm ST depression to 2.0 mm ST elevation) when measured at the J-point ($r=.91$, $p < .001$), and .08 seconds after the J-point ($r=.95$, $p < .001$). FM recording was equally accurate when compared with the standard ECG ($r=.89$, .95 respectively, $p < .001$). Accuracy of the AM and FM systems was independent of RR-interval, R- or S-wave amplitude.

From the ambulatory sessions, the AM technique accurately recorded the number of episodes of ST deviation as recorded by the FM technique (n=24 episodes), as well as the maximum depth of ST deviation (range 0 to 3 mm ST depression, $r=.90$).

Both AM and FM AECGs accurately reproduce ST-segment deviation associated with ischemia. With appropriate modern devices, theoretical concerns about AM AECG do not appear justified.

DO LATE POTENTIALS PREDICT SUSTAINED VENTRICULAR TACHYCARDIA INDEPENDENT OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE?

Thomas A. Buckingham, MD, Sanjay Ghosh, PhD, Robert M. Redd, MD, Bernard R. Chaitman, MD, FACC, Linda Stevens, RN, Harold L. Kennedy, MD, FACC, St. Louis University Medical School, St. Louis, MO

To determine if late potentials (LP) correlate with sustained ventricular tachycardia (VT) independent of left ventricular function, we performed cardiac catheterization and signal averaged ECG recordings on 48 patients with coronary artery disease (10 with documented sustained VT and 38 without). Three criteria for LPs were used; duration of filtered QRS > 120ms (DQ), duration of low amplitude signal > 40ms (DLAS), and amplitude of the last 40ms of the QRS >20 uv (AL40). The diagnostic accuracy of the three LP criteria in indicating patients with sustained VT was:

	SENSITIVITY	SPECIFICITY	ACCURACY	P VALUE
DQ	22%	76%	67%	NS
DLAS	58%	86%	80%	.006
AL40	44%	86%	72%	.03

*(by chi-square)

A stepwise multiple logistic regression model was used to analyze the relation of LP variables, age, left ventricular score, number of disease vessels (>70% stenosis), and presence of left ventricular aneurysm. DLAS was shown as the only significant variable which correlated with sustained VT. These results indicate that late potentials correlate with sustained VT independent of left ventricular function or extent of coronary artery disease.

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #260/261
Variables Affecting Revascularization

PTCA OF DISTAL CORONARY STENOSIS VIA PATENT INTERNAL MAMMARY ARTERY GRAFTS - IMPROVED RECENT EXPERIENCE.
Lee V. Giorgi, M.D.; Geoffrey O. Hartzler, M.D., F.A.C.C.; David R. McConahay, M.D., F.A.C.C.; Barry D. Rutherford, M.D., F.A.C.C.; Warren L. Johnson, M.D., F.A.C.C.
Mid-America Heart Institute, St. Luke's Hospital, Kansas City, Missouri.

Because of technical factors, PTCA of lesions distal to IMA graft anastomosis has been limited. Of a total experience of 4000 PTCA procedures, coronary angioplasty through patent IMA grafts was attempted on 14 lesions in 13 pts. All pts. were male, aged 38-74 (m=56 yrs), with interval from CABG to PTCA of 4 mos to 11 yrs (m=4.0 yrs).

Thirteen lesions were dilated through a left IMA graft and one through a right IMA. Three procedures were single lesion dilatations and 10 were multiple lesion. In 9 pts. the IMA was cannulated with a "heat-reshaped" standard Judkins-style right coronary guide catheter over an exchange wire. In the other 5, a specially-designed "LIMA" guide was used. A standard, fixed-wire, non-steerable, balloon catheter was used in the first 3 pts. (from 6/82-5/83). For the subsequent 11 lesions a flexible,steerable, low-profile balloon was employed.

Two of the first three procedures were failures with one complicated by IMA dissection and hematoma formation requiring urgent CABG, but without myocardial infarction. The subsequent 11 cases were successful (after 5/83) without complications.

Of successfully dilated patients, 11 were asymptomatic or had improved functional class at follow-up of 1-30 mos (m=9.4 mos). One had recurrence of angina resulting from restenosis of a previously-dilated, non-grafted intermediate branch.

We conclude that recent technical advances in PTCA instrumentation have allowed successful and safe angioplasty of distal coronary stenoses via patent IMA grafts.

ARTERIAL BLOOD INFUSION FOR MYOCARDIAL PROTECTION DURING PTCA
Adam D. Timmis, MD, Jonathan C. P. Crick, D Phil, Brian Griffin, MB, Edgar Sowton, MD, FACC.
Guy's Hospital, London, England

Much of the potential risk of PTCA relates to severe myocardial ischaemia during balloon inflation. We have investigated the protective effect of infusing arterial blood through the angioplasty catheter into the distal coronary artery during 60 second dilatations. ECG and echocardiographic indices of regional ischaemia were monitored during dilatations with and without blood infusion. The effect of infusing Hartmans solution was also evaluated to control for washout effects. Ten patients were studied. Dilatations without blood produced chest pain after 22.7 ± 10.2 seconds (SD) in 7 patients and signs of regional ischaemia in every case: echocardiographic dyskinesia occurred within 16.0 ± 3.2 seconds and ST segment elevation (1.9 ± 1.3 mm) within 18.4 ± 6.6 seconds. Blood infusion (45.6 ± 13.4 ml/min) dramatically reduced manifestations of ischaemia: only one patient experienced pain and dyskinesia after 45 and 49 seconds, respectively, though ST segment elevation was observed in 3 cases after 29.3 ± 5.1 seconds. The peak ST change, however, was only 0.8 ± 0.3 mm. In 2 patients severe chest pain and ST segment elevation were reversed by infusing blood. Importantly, infusion of Hartmans solution was unhelpful indicating that delivery of oxygen and not washout of metabolites was responsible for the beneficial effects of blood infusion. These data suggest that the development of PTCA catheter systems which permit blood infusion into the distal coronary artery will improve the safety of the technique. Moreover, by allowing more prolonged periods of balloon inflation a higher success rate can be expected.

VARIABLES AFFECTING SUCCESS RATES IN ANGIOPLASTY (PTCA) OF TOTAL OCCLUSIONS.
Barry Cohen, MD, Craig Monsen, MD, William Schwartz, MD, FACC, Robert Perdoncin, MD, Susan Hosat, MS, Peter Rentrop, MD, FACC. The Mount Sinai Medical Center, New York, NY 10029.

A panel of 2 angiographers, independent of the angioplasty team, analyzed success rates in PTCA procedures involving total occlusions. These lesions were categorized according to the TIMI (Thrombolysis in Myocardial Infarction Trial) classification (T). T(0) is complete obstruction, T(1) is an obstruction with minimal antegrade flow incompletely filling the distal vessel. The population consisted of 69 pts (59 males); mean age was 58. There were 39 T(0) and 30 T(1) patients. T(0) success rate was 47% in the first 19 pts, 51% in the subsequent 20 pts (ns). T(1) success rate was 47% in the first 15 cases, 93% in the subsequent 15 cases ($p < 0.01$). T(1) had a significantly higher success rate than T(0) during the second half of the experience ($p < 0.001$). Funnel-shaped lesions had higher success rates in both groups (68% of 41 pts) than broad-based lesions (43% of 28 pts) ($p < 0.05$). Lesions of less than 12 weeks estimated duration had higher success rates in both groups (64% of 36 pts) than older lesions (29% of 14 pts) ($p < 0.05$). Dissection occurred in 5 T(0) and 11 T(1) pts (p=0.06). One dissection in each group was associated with ischemia requiring CABG. Acute reocclusion occurred in 4 T(0) pts and 1 T(1) pt; it was successfully treated with repeat TCA in each case. There was one asymptomatic side branch occlusion in each group. Conclusions: T(1) lesions can be dilated by an experienced operator with a > 90% success rate; success rates are significantly lower in T(0) lesions. Funnel-shape and occlusion of < 12 weeks are associated with higher success rates in both groups. There is a trend towards higher dissection rates in T(1) lesions and higher reocclusion rates in T(0) lesions.

ST-ELEVATION AS A MARKER OF PRESENCE, EXTENT AND LOCATION OF WALL MOTION ABNORMALITIES DURING CORONARY ANGIOPLASTY.
Marc Cohen, MD, FACC, Steven J. Sharpf, BA, K. Peter Rentrop, MD, FACC, Mount Sinai Med Ctr, New York, N.Y.

Patients (pts) with coronary artery disease undergoing transluminal coronary angioplasty (TCA) are at risk for sudden coronary occlusion and subsequent left ventricular dysfunction. This study assesses the usefulness of different ECG parameters as markers of presence, extent and location of new wall motion abnormalities seen during angioplasty balloon inflation (INF). We prospectively studied 20 pts with isolated LAD(n=11) or RCA(n=9) disease and a normal baseline LV-gram. Using X-ray transparent electrodes, a simultaneous 12-lead ECG was recorded prior to passing the TCA balloon, and another at 30 seconds into the 4th INF cycle. Using a second arterial catheter, an LV-gram was obtained at 40 seconds into the 4th INF. The extent of wall motion abnormalities was described as the % of LV perimeter showing asynergy (Asyn). During INF, 16 of the 20 pts developed new ASYN ranging from 5%-40%. 14/16 pts developed ST elevation (ST↑) while only 10/16 had ST depression (ST↓). Two pts with RCA lesions and new ASYN=5%, had neither ST↑ nor ST↓. ST↑ in V_2 was the most sensitive marker for anterior wall ASYN. ST↑ in L-III was the most sensitive marker for inferior wall ASYN. In pts with LAD TCA, %Asyn correlated with total number of leads (NOL) with ST↑, ≥.5mV, r=.73, magnitude (Mag) of ST↑ in V_2 (r=.73), and ΣST↑ in all 12 leads (r=.62). In pts with RCA TCA, %Asyn correlated with NOL with ST↑, r=.77, Mag of ST↑ in L-III (r=.78), and ΣST↑ in all 12 leads (r=.74). %Asyn did not correlate with the presence or absence of reciprocal ST↓. Conclusion: Acute ST↑ parallels the development of new asynergy during TCA. The association between ST↑ and the extent of asynergy may be useful in predicting the impact of sudden coronary dissection and occlusion on ventricular function.

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MULTIVARIATE ANALYSIS OF CLINICAL, ANGIOGRAPHIC AND EXERCISE TL-201 VARIABLES FOR THE PREDICTION OF RECURRENT ANGINA AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA). Thomas D. Stuckey MD, George A. Beller MD, FACC, Robert S. Gibson MD, Denny D. Watson PhD, Christine L. Tedesco RN, Thomas W. Nygaard MD, FACC, Lawrence R. Burwell MD, FACC. Univ. of Virginia, Charlottesville, VA

We sought to prospectively identify which variables were significant predictors of recurrent angina (RA) after PTCA. Of 62 consecutive post-PTCA pts undergoing quantitative exercise Tl-201 scintigraphy (Ex-Tl) at an average of 2 wks post-PTCA, 53 were asymptomatic prior to ExTl. Of these, 20(38%) developed RA during follow-up; 14 had repeat cath showing restenosis in 11(79%) and distal or side branch stenoses in 3(21%). There was no difference between persistently asymptomatic and RA groups with respect to % stenosis after dilatation (21±16 vs 24±22%), post-PTCA gradient (16±10 vs 14±8 mmHg) or remote stenoses. Sensitivity, specificity and predictive accuracy of Tl-201 redistribution (Rd) for subsequent RA were 40%, 91% and 72%, respectively. For exercise ST↓ values were 35%, 73% and 58%. By stepwise discriminant function analysis of 22 variables, Tl Rd (F=11.49; p=.0017), any ExTl abnormality (F=10.57; p=.0025) and left circumflex disease (F=5.12; p=.03) were the only significant univariate predictors of RA. Age, female gender, presence of distal stenoses, treadmill time, METs achieved, rate-pressure product and exercise ST↓ were not identified as significant. When Tl-201 Rd was included in the model, no further variables were shown to be predictive. Thus, despite a rather low sensitivity, Tl-201 Rd, on early post-PTCA exercise testing was the only significant independent predictor of subsequent recurrent angina during the 1st year of follow-up. Angiographic and other exercise test variables were not predictive.

COMPARISON OF COMPLICATIONS IN PATIENTS WITH PRIOR CORONARY BYPASS GRAFT SURGERY UNDERGOING ANGIOPLASTY OR REPEAT BYPASS SURGERY

Pierre Abi-Mansour, MD, Gary Gershony, MD, Gary Roubin, MB, PhD, Ellis Jones, MD, Andreas Gruentzig, MD, FACC. Emory University School of Medicine, Atlanta, Georgia.

We retrospectively analyzed the in-hospital complications in 316 consecutive patients (pts) who had initial coronary bypass graft surgery (CABG) at Emory Hospital and later required additional myocardial revascularization. Between January 1980 and August 1985, PTCA was performed in 144 pts with suitable anatomy and repeat CABG in 172 pts. In 69 pts (48%), PTCA was performed on stenosed grafts.

The PTCA and repeat CABG pts had comparable clinical profiles: mean age (56 years), men (81%), diabetes (22% vs 23%), hypertension (45% vs 39%), heart failure (11% vs 12%), unstable angina (44% vs 49%). The repeat CABG patients had higher incidence of multivessel disease (88% vs 78%), and complex coronary anatomy including high risk graft stenoses not suitable for dilatation. The incidence of procedure related complications in the 2 groups are tabulated below:

	PTCA (n=144)	Repeat CABG (n=172)
Death	0	5 (2.9%)*
Q-wave MI	2 (1.4%)	8 (4.7%)
Stroke	0	4 (2.4%)
Arrhythmias	5 (3.5%)	36 (20.9%)**
Infection	0	5 (2.9%)*
Reexploration for bleeding	-	7 (4.1%)
Emergency CABG	2 (1.4%)	-

* p<0.05, ** p<0.001

Conclusion: In selected pts with post-CABG progression of native vessel disease or graft stenosis, PTCA may offer a safer alternative to repeat bypass surgery if the coronary anatomy is suitable.

Tuesday, March 11, 1986
4:00PM-5:30PM, Room #260/261
Drugs and Coronary Artery Disease

IS THE ANCILLARY PROPERTY OF ALPHA 1 BLOCKADE OF LABETALOL IMPORTANT?

Xavier E. Prida, M.D., Robert L. Feldman, M.D., F.A.C.C., James A. Hill, M.D., F.A.C.C., Carl J. Pepine, M.D., F.A.C.C. University of Florida, Gainesville, FL

Beta adrenergic blockers are available with various ancillary properties. Advantages of the ancillary property of alpha$_1$-adrenergic blockade were assessed by comparing coronary and systemic effects of Labetalol (L, 0.5 mg/kg IV) and Propranolol (P, 0.1 mg/kg IV) at rest and during supine exercise before and after either P (12 patients) or L (12 patients). At the external work load which evoked angina before beta blockade, both beta blockers usually prevented recurrence of exercise evoked angina (P 8 of 12, L 8 of 12). No adverse effects occurred with either P or L.

	PERCENT CHANGE FROM BEFORE TO AFTER DRUG					
	P	REST	L	P	EXERCISE	L
HR	- 9	*	- 3	-14		-12
MEAN AoP	- 3	*	-10	- 8		-12
LVEDP	+ 6		- 6	+10	*	- 7
CO	-10	*	+10	-23	*	-11
SVR	+ 6	*	-16	+14		- 1
CSF	- 5		+ 3	-15		-20

* p <.05 P vs L

At rest, L consistently decreased AoP and SVR, was more likely to preserve coronary flow and produced less bradycardia than P. The relationship between CO and LVEDP was improved at rest and during exercise by L but not by P.

Thus, the combination of alpha$_1$ blockade and nonselective beta blockade (i.e. L) offers potential hemodynamic advantages as compared to nonselective beta blockade alone (i.e. P).

EFFECT OF HUMAN CORONARY OCCLUSION ON THROMBOXANE A2 AND LEUKOTRIENE C4 RELEASE

Jawahar L. Mehta, M.D., F.A.C.C., Robert L. Feldman, M.D., F.A.C.C., Robert G. Macdonald, M.D., Gordon Letts, Ph.D., University of Florida, Gainesville, FL., and Merck-Frost, Dorval, Canada.

Release of coronary spasmogens and thrombogenic stimuli such as thromboxane A2(TxA2) and leukotriene C4(LTC4) during PTCA may contribute to acute coronary occlusion or during follow-up to restenosis. To determine potential contribution of TxA2 and LTC4, we measured pulmonary artery(PA) and great cardiac vein(GCV) TxB2 (stable metabolite of TxA2) and LTC4 (both by specific radioimmunoassay) in 5 patients undergoing LAD PTCA. Paired plasma samples were collected before, during and 30 sec after balloon occlusion. Patients were pretreated only with aspirin.

During balloon inflation each patient had angina and ST shifts and GCV flow values decreased an average of 39% at the site adjacent to GCV blood sampling. PA plasma TxB2 remained unchanged (< 50 pg/ml) but GCV plasma TxB2 levels increased from <50 pg/ml prior to balloon inflation to 132±44 pg/ml (mean ± SD, p <.05) during balloon occlusion and to 174±52 pg/ml during reperfusion. LTC4 levels in GCV plasma were in the normal range (0.60±0.20 ng/ml;peripheral enous plasma from normal subjects 1.0±0.1 ng/ml) and were unchanged during balloon occlusion (0.75±0.26 ng/ml) or during reperfusion (0.58±0.20 ng/ml). PA plasma LTC4 levels were also unaffected by LAD occlusion.

In conclusion, LTC4 levels (PA and GCV) in CAD patients are similar to values in clinically healthy subjects, and do not change during acute coronary occlusion or reperfusion. In contrast, even in aspirin-treated patients, coronary venous TxB2 levels increase during coronary occlusion. Vascular TxA2 release occurs during PTCA.

DISPARATE EFFECTS OF NICARDIPINE ON EXERCISE AND PACING INDUCED ISCHEMIA

Charles R. Lambert, M.D., Ph.D, James A. Hill, M.D., FACC, and Carl J. Pepine, M.D., FACC, University of Florida, Gainesville, FL

To further define the anti-ischemic effects of nicardipine, a new dihydropyridine calcium antagonist, systemic and coronary hemodynamics were investigated in 17 coronary artery disease patients (pts). Heart rate (HR),systolic pressure (SP), coronary sinus flow (CSF), and myocardial oxygen consumption (MVO_2) were measured before and during pacing or exercise induced angina. Studies were repeated during nicardipine (2 mg bolus followed by continuous IV infusion titrated to reduce SP 10 mmHg). A similar decline in SP was achieved in pts undergoing both forms of stress. Exercise-induced angina, however, which occurred in each pt before nicardipine, was prevented in 8 of 10 pts at the same level of exercise stress after nicardipine. During exercise, nicardipine reduced the rise in SP (-9.4%, $p < 0.05$) and permitted increased exercise before angina associated with increases in CSF (20%, $p < 0.05$), HR (14%) and MVO_2 (10%). Angina was not prevented by nicardipine during pacing stress to the same HR, despite a reduction in SP (-9.7%) and MVO_2 (-17%, both $p < 0.05$). These data suggest that nicardipine has very complex coronary and systemic hemodynamic effects. With exercise, nicardipine induces systemic and coronary vasodilation which reduces SP and decreases O_2 demand, thus delaying angina and allowing higher CSF. However, during pacing, nicardipine induces vasodilation which reduces SP similarly but does not prevent angina. This suggests that nicardipine influences other factors important in exercise-induced angina, but not operative in pacing induced angina.

EFFECT OF HEPARIN ON INTRACORONARY THROMBI IN UNSTABLE ISCHEMIC SYNDROMES.

Daniel Hartman,B.A., Nelson M. Wolf,M.D.,F.A.C.C., Jay A. Shechter, M.D., Alexis B. Sokil,M.D., Gaetano Capone, M.D., Steven G. Meister, M.D.,F.A.C.C.. Medical College of Pennsylvania, Philadelphia, Pennsylvania.

Intracoronary thrombi (ICT) are common in patients with unstable ischemic syndromes (UIS), i.e., unstable angina and non Q wave myocardial infarction (MI). Heparin has been reported to reduce the incidence of progression to transmural MI in such patients. To determine whether heparin promotes lysis of ICT, we reviewed angiograms of 14 UIS patients who received a course of heparin prior to a second angiogram and 13 non-randomized control UIS patients who did not receive heparin. All had ICT on initial angiograms. Second angiograms were usually performed for angioplasty. The interval between first and second angiograms was 22.6±5.1 days for heparin patients and 18.1±5.0 days for controls (p=NS). Angiograms were examined by two blinded observers or a third in case of disagreement. Patients were considered improved if ICT disappeared or were reduced in size and unimproved if ICT were unchanged or became larger or if the associated stenosis progressed to total occlusion. Ten of 14 heparin patients improved in contrast to 0 of 14 controls ($p<0.0001$), as detailed below:

		ICT		ICT	ICT
	Occluded	Larger	No Δ	Smaller	Disappeared
Heparin pts.	2	0	2	5	5
Controls	7	2	4	0	0

Thus, an increased incidence of ICT clearing was observed in patients who received heparin. These findings support use of therapeutic heparinization in UIS patients.

CAN INTRACORONARY THROMBOLYSIS PREVENT FREE WALL RUPTURE OF ACUTE MYOCARDIAL INFARCTION?

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To evaluate the influence of intracoronary thrombolysis on the incidence of ventricular free wall rupture complicating acute myocardial infarction (AMI), 490 patients (pts) were analyzed; Group A pts (n=300) underwent intracoronary thrombolysis, and Group B pts (n=190) did not. Free wall rupture occurred in 11 of Group A pts (11/300 = 3.3% : 9/156 with anterior AMI and 2/144 with inferior AMI), and 13 of Group B pts (13/190 = 6.2% : 9/119 with anterior AMI and 4/71 with inferior AMI). The mean interval from the onset of ischemic pain to the rupture event was 14 ± 11 hours (mean ± SD) for Group A, and 79 ± 63 hours for Group B pts ($p < 0.05$). The 156 pts of Group A with anterior AMI on whom coronary angiography was available, were subdivided into 2 subsets according to the presence or absence of collaterals. No rupture was observed in pts (n=37) with evidence of collaterals. Out of 114 pts with no collaterals, intracoronary thrombolysis was successful in restoring sufficient antegrade flow in 46 pts, and unsuccessful in the remaining 68 pts. Free wall rupture occurred in 8/68 (11.8%) pts with no restoration of flow, and in only 1/46 (2.2%) pts with successful intracoronary thrombolysis ($p < 0.1$).
Thus, a) successful intracoronary thrombolysis decreases the incidence of free wall rupture in AMI, but b) free wall rupture, if it does occur, occurs significantly earlier in pts subjected to intracoronary thrombolysis.

CORONARY MORPHOLOGY FOLLOWING STREPTOKINASE IN MYOCARDIAL INFARCTION AND UNSTABLE ANGINA. A CLUE TO PATHOGENESIS.

John A. Ambrose MD,FACC, Craig Monsen MD, Stephen Winters MD, Rohit Arora MD, K. Peter Rentrop MD, FACC, Deborah Rudin BS, Susan Maratea BS, Jacob Haft MD, FACC, Richard Gorlin MD, FACC, Valentin Fuster MD, FACC. Mt. Sinai Hospital, NY, NY.

We have shown that eccentric stenoses with overhanging edges and/or irregular borders (E_2) are seen in 2/3's of patients with either unstable angina or infarction (AMI) and < 100% occluded ischemia related vessels but rarely in stable angina. Plaque disruption and thrombus seen pathologically in AMI may explain this morphology. To further study E_2, 37 patients with AMI or unstable angina received intra-coronary streptokinase (SK). Gr.I had 17 with AMI and 100% occluded vessels recanalized with SK. Gr.II had 10 with AMI and < 100% infarct vessels pre SK. All were studied acutely (< 12 hrs. after AMI) and 17 in Gr.I and 6 of 10 in Gr.II were restudied chronically (1-10 wks.) Gr.III had 10 with unstable angina and < 100% occluded ischemia vessels pre SK and 6 of 10 were restudied.

	ACUTE			CHRONIC		
Gr(number)	I(17)	II(10)	III(10)	I(17)	II(6)	III(6)
< 100% E_2 (post SK)	10	7	8	1	4	3
< 100% Non-E_2	7	3	2	4	2	2
100% Stenosis	0	0	0	6	0	1
< 50% Stenosis	0	0	0	6	0	0

Following SK, 10 of 17 lesions >50 < 100% in Gr.I were E_2 versus 15 of 20 in combined Gr.II and III (p=ns). No lesion in Gr. II or III changed morphology acutely with SK. Chronically, 1 of 17 remained E_2 in Gr. I versus 7 of 12 in Gr.II and III ($p < .01$). This change was independent of SK dose and heparinization. Thus, thrombus superimposed on plaque rupture may explain the changing morphology in AMI and recanalized 100% vessels. Plaque disruption with or without a minor thrombus may account for the more stable morphology in initially < 100% occluded ischemia related vessels in AMI or unstable angina.

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #360/361
Clinical Effects of Local Anesthetic Antiarrhythmic Drugs

STEREOSELECTIVE PHARMACOKINETICS AND PHARMACODYNAMICS OF DISOPYRAMIDE IN MAN.

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Ohio State University University, Columbus, Ohio.

Adverse effects on left ventricular (LV) function of disopyramide could be minimized by exploiting the stereoselective properties of the drug. To test this thesis in 5 healthy males, we randomly infused 100 mg of S(+) and R(-) disopyramide intravenously over 20 minutes on two occasions separated by one week. Heart rate, corrected electrical systole (QTI), pre-ejection period (PEPI), LV ejection time (LVETI), PEP/LVET and plasma concentrations (PC) were measured before, during and for 5 hours post infusion. The serum protein binding of S(+) disopyramide was higher than that of the R(-) enantiomer at similar unbound concentrations. The unbound clearance of S(+) disopyramide was higher and its half-life shorter as compared to the R(-) enantiomer (604 ml/min vs 401 ml/min and 3.67 vs 4.62 hours respectively). The unbound renal clearance of S(+) and R(-) disopyramide averaged 338 and 182 ml/min respectively. Maximal changes (Δ) are shown. *p<0.05 between S(+) and R(-).

	ΔQTI	ΔPEPI	ΔLVETI	ΔPEP/LVET
S(+)	56±4*	22±5*	2±2*	.06±.02*
R(-)	9±2	40±7	-26±5	.17±3

Responses were fitted to the Hill equation; differences in response were not due to differences in unbound plasma concentration. Different effect on QTI, PEPI, LVETI and PEP/LVET by S(+) and R(-) enantiomers of disopyramide suggest different electrophysiologic effect (QTI) and different effect on LV performance (PEPI, LVETI, PEP/LVET). Thus the pharmacokinetics and pharmacodynamics of S(+) and R(-) of disopyramide are stereoselective.

IMPACT OF VENTRICULAR DYSFUNCTION ON RESULTS OF FLECAINIDE THERAPY FOR VENTRICULAR TACHYCARDIA

Angelo A.V. DePaola, M.D., Sheila Senior, R.N., Joel Morganroth, M.D., F.A.C.C., Scott R. Spielman, M.D., F.A.C.C., Allan M. Greenspan, M.D., F.A.C.C., Leonard N. Horowitz, M.D., F.A.C.C., Likoff Cardiovascular Institute, Philadelphia, PA.

To evaluate the clinical impact of flecainide's (FLEC) negative inotropic potential, we studied 87 patients (pts) with sustained (43 pts) and nonsustained (44 pts) ventricular tachycardia (VT). All pts had baseline radionuclide left ventricular ejection fraction (EF) measured off antiarrhythmic drugs and heart failure (CHF) optimally managed before FLEC. FLEC was orally titrated from 100 mg bid in 50 mg increments at 4 day intervals in hospital. The mean dose was 150 mg bid and mean plasma level was 720 ng/ml. Before FLEC, compensated CHF (CHF-old) was present in 26 pts (8 pts with EF>30, 18 pts with EF≤30). On FLEC, 0/49 pts with EF>30 had new or worsened CHF. New or worsened CHF occurred in 8/38 pts with EF≤30, 7 with CHF-old and 1 without CHF-old. During FLEC, 6/8 pts with Class III CHF (all had EF≤30) had worsening of CHF and 4 died. Clinical efficacy and tolerance of FLEC at 6 mos of therapy was 57% (28/49) in pts with EF>30 and 21% (8/38) in pts with EF≤30 (p<0.05). We conclude that: 1) CHF can occur during FLEC therapy particularly in pts with CHF-old and EF≤30 and may particularly limit therapy in pts with severe CHF; 2) clinical efficacy and tolerance of FLEC is significantly lower in pts with EF≤30.

COMBINATION OF PROCAINAMIDE AND ATRIAL PACING FOR SUCCESSFUL CONVERSION OF ATRIAL FLUTTER TO SINUS RHYTHM

Brian Olshansky, M.D., Ken Okumura, M.D. Richard W. Henthorn, M.D., F.A.C.C., Andrew E. Epstein, M.D., F.A.C.C., Vance J. Plumb, M.D., F.A.C.C., Albert L. Waldo, M.D., F.A.C.C., University of Alabama at Birmingham, Birmingham, Alabama.

Rapid atrial pacing is a useful technique to terminate atrial flutter. However, in many patients, interruption of atrial flutter by this method results in atrial fibrillation. We studied 9 patients who had atrial flutter with a mean cycle length of 243±30 ms in whom rapid atrial pacing was performed during atrial flutter from 1 site (high RA) in 2 patients, 2 sites (high RA, coronary sinus) in 3 patients, and 3 sites (high RA, coronary sinus, low RA) in 4 patients. Pacing for at least 15 sec was initiated at a cycle length 10 ms less than the atrial flutter cycle length from each site. After termination of rapid atrial pacing, if atrial flutter persisted, rapid atrial pacing was repeated, decreasing the cycle length in steps until reaching a cycle length of 160 ms. If atrial flutter continued, then a second, and, if necessary, a third site was paced. In all patients, atrial flutter was initially entrained by rapid atrial pacing. Then rapid atrial pacing at faster rates resulted in conversion to sinus rhythm in 2 patients, sustained atrial fibrillation in 1 pt, and transient atrial fibrillation with resumption of atrial flutter in the other 6 patients. Intravenous procainamide was given to these later 6 patients (1000 mg to 4 patients and 500 mg to 2 patients) increasing their mean atrial flutter cycle length from 250±28 to 314±43 ms. Then, using the same rapid atrial pacing protocol, high RA pacing at an average cycle length of 235±65 ms interrupted atrial flutter, successfully converting the rhythm to sinus in all patients without induction of atrial fibrillation. Thus, intravenous procainamide augments the efficacy of rapid atrial pacing used to convert stable atrial flutter to sinus rhythm in patients.

COMBINATION OF LOW DOSE QUINIDINE AND TOCAINIDE IN THE TREATMENT OF VENTRICULAR ARRHYTHMIAS IN MAN.

Jean T. Barbey, MD, Katherine A. Thompson, MD, Debra S. Echt, MD, FACC, Raymond L. Woosley, MD, PhD, Dan M. Roden, MD, FACC. Vanderbilt University, Nashville, TN.

Selected antiarrhythmic combinations are beneficial in the treatment of patients with ventricular arrhythmias (VA). We evaluated tocainide (T) and quinidine (Q) singly and in combination in 14 patients (age 60±9 years), all with chronic VA (508±627 VEDs/hr $\bar{x}$±SD), and 12/14 with runs of nonsustained ventricular tachycardia (VT) (1-1712/24 hrs). After 2 days of placebo (PL), therapy was administered in 4 consecutive 3 day phases: T 1200 mg/day; followed by titration to 1800 or 600 mg/day based on arrhythmia control and side effects; addition of Q gluconate 972 mg/day to the titrated dose of T; Q alone. Three patients could not complete the study because of intolerable side effects (2 Q, 1 T). VA were considered suppressed if reduced in frequency by >70% and VT reduced by >90%.

	PL	T600	T1200	T1800	Q	T+Q
VA Suppression	0/11	0/3	3/11	3/8	3/11	6/11
Side Effects	0/11	0/3	3/11	3/8	1/11	2/11
QTc (msec)	449±42		429±24		496±37*	479*34*

* Different from PL and T1200 (p<.05, 2 way ANOVA)

Two patients were discharged on single therapy (1Q, 1T), six on T+Q and three on T+dose-adjusted Q. Of the nine discharged on T+Q combinations, two later required reduction of T dosage due to side effects. (Follow-up = 7±3 months.)

Conclusions: Quinidine and tocainide were comparably effective agents although dose related side effects were more frequent with tocainide. Adding quinidine to tocainide decreased toxicity and enhanced tocainide's efficacy. While the two drugs exerted additive antiarrhythmic actions, they produced antagonistic effects on repolarization. This suggests that the combination may be clinically useful and exerts pharmacologic actions unlike those of either single agent.

COMBINED MEXILETINE/CLASS 1A TREATMENT OF REFRACTORY VENTRICULAR ARRHYTHMIAS - LONG-TERM RESULTS.

Brian McGovern, M.B., Eric N. Whitford, M.B., Mark H. Schoenfeld, M.D., Hasan Garan, M.D., Mary McElroy, Jeremy N. Ruskin, M.D., F.A.C.C. Massachusetts General Hospital, Boston, Massachusetts

It has been demonstrated that a combination of mexiletine (M) and a class 1A antiarrhythmic drug (AAD) may suppress ventricular tachycardia during serial electrophysiologic studies in approximately 30% of patients (pts) with ventricular tachycardia refractory to Class 1A AAD and M alone. The long-term efficacy and tolerance to such a regimen is unknown however. We evaluated combination AAD therapy in 106 pts. Twenty-nine pts had prior cardiac arrest, 46 pts had spontaneous sustained ventricular tachycardia and 31 pts had symptomatic nonsustained ventricular tachycardia or syncope. The mean ejection fraction was 32±15%. Ventricular tachycardia was induced by programmed cardiac stimulation (PCS) in all pts in the absence of AAD. Spontaneous or PCS-induced ventricular tachycardia occurred in all pts during treatment with Class 1A AAD and with M alone. Combination of 1A AAD and M suppressed ventricular tachycardia in 32/106 pts (30%). Sixty-five pts were discharged on combination AAD and followed from 1-6 years. Fourteen/65 pts (22%) have suffered recurrent ventricular tachycardia or died suddenly. Actuarial freedom from recurrent ventricular tachycardia is 86% at 1 year, and 72% at 5 years. In 11 of 65 pts (17%) one or both drugs had to be discontinued because of adverse effects. We conclude that in patients with inducible ventricular tachycardia refractory to Class 1A AAD and M alone, a combination of 1A AAD plus M, 1)suppresses ventricular tachycardia in 30% of pts 2) provides effective long-term prophylaxis against recurrent ventricular tachycardia, and 3) is limited by intolerable side effects from either drug in 17% of pts.

EFFICACY OF INTRAVENOUS PROPAFENONE IN PATIENTS WITH W-P-W-SYNDROME

Paul L. Ludmer, M.D., Elliott M. Antman, M.D., FACC, Peter L. Friedman, M.D., Ph.D. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Intravenous (I.V.) propafenone (P) was studied in 11 patients (pts) with W-P-W syndrome in a double-blind placebo-controlled trial. Atrial (A), ventricular (V) and accessory pathway (AP) effective and functional refractory periods (ERP, FRP in ms.) were measured in all pts before P. Control characteristics during circus-movement tachycardia (CMT) and peak V rate (VR) during atrial flutter or fibrillation (AF) were determined. All parameters were measured again after placebo and after P 2 mg/kg. Placebo had no effect on A, V or AP ERP or FRP, and never caused termination of CMT or slowed the VR during AF. P lengthened A-ERP (220±20 to 275±20), A-FRP (278±18 to 315±11), V-ERP (240±10 to 262±9), antegrade AP-ERP (298±35 to 525±82) and retrograde AP-ERP (255±28 to 496±66) ($p < .05$). P promptly terminated CMT in 10/11 pts due to retrograde block in the AP in 8/10 and antegrade block in the A-V node in 2 pts. After P, sustained CMT was not inducible in 10/11 pts. After P, peak VR during AF was much slower (231 beats/min to 145 beats/min $p < .05$). Peak VR never increased. In 6 pts P caused spontaneous termination of AF.

We conclude: I.V. P is a safe, rapidly acting agent that effectively terminates CMT and slows VR during AF in pts with W-P-W syndrome.

Tuesday, March 11, 1986
4:00PM-5:30PM, Room #360/361
Amiodarone

EFFECTS OF AMIODARONE ON SYMPATHETIC AND PARASYMPATHETIC CONTROL OF HEART RATE IN MAN.

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Amiodarone (AM) slows sinus heart rate (HR) in man and produces noncompetitive adrenergic inhibition experimentally. Since the autonomic actions of AM may influence its antiarrhythmic efficacy, we examined the effect of AM on sympathetic and parasympathetic control of HR in 7 men, aged 45 to 65 yrs, treated with AM for control of ventricular (5) or supraventricular (2) tachycardia. Five patients (pts) had ischemic heart disease and 2 pts had no apparent disease: all were normotensive, euthyroid and received no other drugs. Autonomic testing was performed at control (C) and after 1 week of AM, 1600 mg/day. Parameters measured were: isoproterenol dose by iv bolus required to increase HR 25/min (CD_{25}) in 7 pts, HR response to 0.15 mg/kg iv propranolol (P) and 0.03 mg/kg iv atropine (A) in 6 pts, and carotid baroreflex increase in sinus cycle length (SCL) due to neck collar suction (NCS) of -60 mmHg for 600 msec applied at 40 msec increments through the cardiac cycle in 5 pts. CD_{25} increased from 2.68±2.39 at C to 8.90 ±10.93 following AM ($p<.05$). From C to AM the HR at rest, 63±7 to 58±4, following P, 57±7 to 51±3, and after P and A, 75±7 to 61±7, were all significantly lower ($p<.01$). The HR decrease after P was similar at C, 7±3 and after AM, 7±2, as was the increase in HR after A, 18±10 and 10±5, respectively. Changes in CD_{25} did not correlate with response to P or P and A. In 2 of 5 pts AM attenuated the maximal SCL increase produced by NCS by 40 and 50 msec each while 3 pts had ≤20 msec change. We conclude that amiodarone significantly inhibits the chronotropic response to beta-adrenergic stimulation and decreases intrinsic HR, but minimally alters resting vagal and adrenergic effects on HR or reflex vagal slowing of HR.

ELECTROPHYSIOLOGIC PREDICTORS OF LONG TERM OUTCOME WITH AMIODARONE FOR REFRACTORY VENTRICULAR TACHYCARDIA.

Charles I.Haffajee,MB,MRCP,FACC, Robert L.Gold,MD, Yoshizumi Yazaki,MD,Kathy Sloan,RN,Joseph S.Alpert,MD, FACC. Univ.Mass.Medical Center,Worcester,MA.

Fifty-six patients(pts) with symptomatic and inducible ventricular tachycardia(VT) refractory to conventional antiarrhythmic agents had programmed ventricular stimulation(PVS) before and after ≥4 weeks of high dose oral amiodarone.All 56 pts were maintained on oral amiodarone (mean 360mg/day) during a mean followup of 22.5 months (Range 2-45 months).

Results:VT was suppressed in 9 of 56 pts(16%)on amiodarone(Group A).Of the 47 pts whose VT remained inducible on amiodarone, 23 pts(51%)had > 25% slowing of VT rate or conversion to nonsustained VT during PVS(Group B)whereas the remaining 24 pts(Group C) had no change in VT rate or had VT exacerbation during PVS.The outcome of all 56pts during followup is shown below:

	# of pts	Pts with VT recurrence	Pts with Sudden cardiac death
Group A	9	0	0
Group B	23	3	2
Group C	24	13	7

Statistical analysis reveals that Group C differs significantly from Group A and Group B($p<.05$).

Conclusions:1)VT remains inducible on amiodarone in most pts(84%) with refractory symptomatic VT.2)VT suppression by amiodarone during PVS results in good long term prognosis.3)Pts whose VT remains inducible on amiodarone appear to form 2 groups;those with VT slowing or conversion to nonsustained VT generally do well whereas those in whom the VT rate is unchanged or exacerbated have a poor prognosis.

AMIODARONE PLASMA CONCENTRATIONS: RELATIONSHIP TO ELECTROPHYSIOLOGIC EFFECTS, EFFICACY AND TOXICITY. Mark L. Greenberg MD, Bruce B. Lerman MD, Tracey Cook, James R. Shipe PhD, John P. DiMarco MD, PhD, FACC. University of Virginia Medical Center, Charlottesville, Virginia.

The value of monitoring amiodarone plasma concentrations is unclear. Forty consecutive patients with coronary disease and sustained ventricular tachyarrhythmias (VT) underwent electrophysiologic studies 29±15 days after initiation of therapy. There was no correlation ($r<0.5$) between amiodarone (1.39±1.16 µg/ml) and desethylamiodarone levels (0.84±0.27 µg/ml) and changes in sinus cycle length, QTc, ventricular effective refractory period, AH and HV intervals, and VT cycle length. Neither higher drug levels nor more pronounced electrophysiologic effects identified the 9 patients whose arrhythmias were no longer inducible by programmed stimulation. The relationships between amiodarone plasma concentrations and toxicity and efficacy were propsectively assessed in a cohort of 113 patients treated with amiodarone (354±105 mg/day) for 9 ±8 months. Excluding patients with common but minor side effects (e.g., corneal deposits and photosensitivity), 50 patients (44%) had adverse effects. Asymptomatic liver enzyme elevations and subclinical hypothyroidism were the adverse effects most frequently seen. Neither amiodarone (1.77±1.03 µg/ml) nor desethylamioadrone plasma concentrations (1.38±0.55 µg/ml) during chronic therapy were related to any adverse effects except elevated liver enzymes. Amiodarone plasma concentrations and dosage also did not differ between effectively (81%) and ineffectively (19%) treated patients.

We conclude that monitoring amiodarone and desethylamiodarone levels is not helpful for assessing electrophysiologic effects or antiarrhythmic efficacy and is of limited value in predicting clinically significant toxicity.

FAVORABLE PROGNOSIS OF AMIODARONE TREATED PATIENTS WITH NONINDUCIBLE VENTRICULAR TACHYCARDIA

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The utility of programmed ventricular stimulation (PVS) in patients (pts) with sustained ventricular tachycardia (VT) treated with amiodarone (Am) is controversial. Forty-seven patients (mean age 61), 14 with sudden death (SD) and 33 with VT, were studied by PVS during control and 2 weeks after oral Am (1400 mg. loading qd. x 7 d., then 400-600 mg. qd. for 7 d.). They were classified clinically by NYHA class and ejection fraction (mean 32.2%). Electrophysiologic parameters (EP) analyzed included sinus node function, AV nodal function, AH, HV, ventricular refractory period (VRP), mode of induction of VT (IND), VT cycle length (CL), change in VRP, change in IND, change in VT-CL. Follow-up was 1-40 mo. (mean 12.7 mo.). Fourteen of the 47 pts (30%) had recurrent VT (mean 9.2 mo.), and 9 (19%) had SD (mean 11.5 mo.). During the post-Am PVS, 37 pts remained inducible (79%) and 10 were noninducible (21%). Seventeen of the 37 inducible pts died (46%); 8 from SD, 7 from other cardiac causes, and 2 from noncardiac causes. Thirteen of the 37 (35%) had recurrent VT. One of 10 noninducible pts (10%) died suddenly and 1 (10%) had recurrent VT. By Probable Hazards Multiple Regression Analysis, there were no clinical or EP variables of statistical significance in prediction of outcome. However, 8 of 10 noninducible pts are alive without recurrent VT or SD. We conclude that noninducibility portends the most favorable prognosis in VT pts treated with Am.

COMBINED EFFECTS OF AMIODARONE AND PROCAINAMIDE IN PATIENTS WITH VENTRICULAR TACHYCARDIA

Francis E. Marchlinski, MD, FACC, Alfred E. Buxton, MD, FACC, Belinda Flores, MSN, Darlene Pembrook-Rogers, Mark E. Josephson, MD, FACC, Univ. of PA, Phila., PA

Most ventricular tachycardia (VT) remains inducible after amiodarone (A) or procainamide (P). To evaluate the combined effects of A and P, 30 patients with VT underwent programmed stimulation in the control state, after P-15 mg/kg with level 9.0±28 µg/ml, on day 14±3 of A alone, 1400 mg/day x 7 days then 400 mg/day and after A with P-15 mg/kg with level 7.7±2.7 µg/ml. All VT was inducible after A alone and P alone. Results expressed as a change (Δ) from control study: mean±SD; Δ VT MORPHOLOGY=different or additional VT morphology

	P	A	A with P
ΔRV REFRACTORINESS(ms)*	+24±12	+21±17	+37±16†
ΔVT CYCLE LENGTH (ms)*	+65±25	+56±25	+107±45†
ΔVT MORPHOLOGY	16	15	15

† $p<.01$ compared to P alone or A alone
* RV refractoriness compared at same rate and VT cycle length compared only if VT had same morphology

Patients with a Δ in VT morphology after P had a Δ in morphology after A (13/16 patients, $p<.01$) and after A with P (11/16 patients, $p<.05$). The sum of the effect of A alone plus P alone on VT cycle length correlated with ($r=.86$, $p<.01$) Δ in VT cycle length after A with P. The Δ in VT cycle length was not related to the Δ in refractoriness for A, P, or A with P ($-.2>r<.1$). A with P prevented VT induction in 1 patient. We conclude: 1) a Δ in induced VT morphology after A, P, and A with P is common and occurs in the same patients; 2) the Δ in VT cycle length after A with P can be predicted by summing the Δ in cycle length after A alone and P alone and is not directly related to measurable effects on refractoriness; and 3) A with P does not prevent VT induction if VT induced on A alone and P alone.

EFFICACY AND TOLERANCE OF AMIODARONE: SPECIAL REFERENCE TO CONGESTIVE HEART FAILURE

Angelo A.V. DePaola, M.D., Patricia M. Brady, R.N., Allan M. Greenspan, M.D., F.A.C.C., Scott R. Spielman, M.D., F.A.C.C., Joel Morganroth, M.D., F.A.C.C., Leonard N. Horowitz, M.D., F.A.C.C., Likoff Cardiovascular Institute, Philadelphia, PA

To evaluate the clinical efficacy and tolerance (CET) of Amiodarone (AMIO) in patients (pt) with ventricular arrhythmias and severe ventricular dysfunction we evaluated 149 pt with sustained (130 pt) and nonsustained (19 pt) ventricular tachycardia, with regard to radionuclide left ventricular ejection fraction (EF), presence of congestive heart failure (CHF), before (CHF-old) or during therapy (CHF-on) (either worsening of CHF-old or new onset of CHF). AMIO loading (1000 mg X 7 da, 800 mg X 7 da, 600 mg X 3 months) was followed by maintenance doses of 200 - 600 mg/da; mean plasma level of 1,7 mcg/ml. Results after 1 year:

		SURVIVAL(%)	RECURRENCE(%)[1]	CET(%)[2]
EF ≤ 30	(102 pt)	80	30	57*
EF > 30	(47 pt)	91	17	76
CHF-old	(55 pt)	78	25	63
NO CHF-old	(94 pt)	87	26	78
CHF-on	(21 pt)	57*	66*	23*
NO CHF-on	(128 pt)	88	19	70
All pt	(149 pt)	83	26	63

* $p < 0,05$ [1] clinical arrhythmia or sudden death
[2] no recurrence, death or toxicity

We conclude: 1) severe ventricular dysfunction can limit AMIO therapy; 2) the occurrence of CHF during AMIO therapy can importantly decrease the CET of this drug.

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #366/367
Hypertensive Heart Disease

THE RELATIONSHIP OF BLOOD PRESSURE AND BODY SIZE TO ECHOCARDIOGRAPHIC MEASURES IN CHILDREN: BOGALUSA HEART STUDY.
Gregory L. Burke, M.D., Walter S. Culpepper, M.D., F.A.C.C., Larry S. Webber, Ph.D., Yu K. Chiang, Ph.D., Rene A. Arcilla, M.D., F.A.C.C. and Gerald S. Berenson, M.D., F.A.C.C. National Research and Demonstration Ctr.--Arteriosclerosis, LSUMC, New Orleans, Louisiana.

Studies in children show that essential hypertension clearly begins early in life. Echocardiographic observations suggest a relatively early response of the heart to hypertension. M-mode echocardiograms were obtained on 651 children, 7-22 years of age, from a total pediatric community. All participants' diastolic blood pressure rank remained in the same height-race-sex specific decile during two consecutive Bogalusa school surveys. Standard echocardiographic measures of heart size increased with age, blood pressure and body size in these growing children. Body surface area and ponderosity (weight/height^3) were found by multiple regression analyses to be the most appropriate covariates for use in adjustment of echocardiographic measurements for body size and age. Males of both races demonstrated significantly higher left ventricular (LV) mass, LV wall thickness and LV chamber size. No consistent racial differences in adjusted LV size were noted. A significant positive correlation was present between systolic blood pressure and LV wall thickness in systole ($r=0.42$, $p<0.001$), which remains even after adjustment for body size ($r=0.21$, $p<0.001$). Measures of LV wall thickness increased throughout the entire blood pressure distribution. Adjusted LV wall stress was significantly related to both systolic and diastolic blood pressure levels ($r=0.37$, $p<0.001$; $r=0.27$, $p<0.001$, respectively). These data demonstrate the heart as an early target organ to respond during the early natural history of hypertensive disease.

CATECHOLAMINE-INDUCED HYPOKALEMIA AND CARDIAC ARRHYTHMIAS
Vasilios Papademetriou, M.D., Aldo Notargiacomo, Ross D. Fletcher, M.D., FACC, Edward D. Freis, M.D., FACC, VA and Georgetown University Medical Centers, Washington, D.C.

Catecholamines can cause a shift of potassium (K) intracellularly, but the arrhythmogenic significance of this change is not known. In this study programmed stimulation (PS) was performed in 8 Mongrel dogs at baseline, and after infusion of epinephrine (EP) 0.1 (A) 0.45 (B) 1.5 (C) or 3.8 μg/kg/min (D). Plasma K (PK) was measured prior to each PS. Following induction of ventricular fibrillation (VF) PK was corrected by infusion of KCl 0.5 mEq/min for 10 minutes while EP infusion continued. The same protocol was repeated following hydrochlorothiazide (H) 100 mg daily for 2 weeks. Changes in PK were as follows:

EP (μg/kg/min)	-	0.1	0.45	1.5	3.8
PK Prior to H (mEq/L)	3.4(8) ±0.4	2.7(8) ±0.3	2.3(4) ±0.2	2.4(2) ±0.1	2.1(2)*
PK after H (mEq/L)	3.4(8) ±0.4	2.6(8) ±0.3	2.0(4) ±0.3	2.2(2) ±0.1	2.0(1)*

*In ( ) number of dogs. $P<0.01$ for all values of PK compared to baseline. Prior to H VF was induced in 2 dogs at baseline, 2 with dose A of EP 2 with B and 1 with C. One dog was not inducible. Following H therapy VF was induced in 2 dogs at baseline 3 with dose A, 2 with B and 1 with C. At the time of VF prior to H, PK averaged 2.4±0.3 mEq/L. KCl infusion increased PK to 3.6±0.3 mEq ($P<0.001$). Of the 7 dogs with VF 6 were still inducible. After H therapy at the time of VF PK averaged 2.3±0.4. KCl increased PK to 3.5±0.5 mEq/L. Of the 8 dogs with inducible VF 7 were still inducible. In conclusion 1) EP infusion caused marked hypokalemia in normal dog; 2) H in the doses used did not affect PK significantly; 3) Titrated doses of EP infusion increased myocardial vulnerability which was not affected by PK correction.

DOES HYPERTENSIVE HYPERTROPHY CAUSE MYOCARDIAL ELECTRICAL INSTABILITY.
David Tepper, Mary Ann Sarda, Joseph M. Capasso, Ph.D., Herman Kleinbaum, Sharon Williams and John C. Somberg, M.D. Albert Einstein College of Medicine, New York.

Myocardial hypertrophy is often associated with a higher incidence of sudden death. To characterize the increased vulnerability ventricular hypertrophy may afford we studied the incidence of arrhythmias following coronary artery occlusion in 11 rats with hypertensive hypertrophy. These results were contrasted to the findings in 14 rats without heart enlargement. Myocardial hypertrophy was produced by constriction of the left renal artery with a silver clip. Hypertension developed in these clipped animals within 2 to 3 weeks and remained at this level until time of study (10 weeks later). Animals were anesthetized with pentobarbital (60 mg/kg) and respired on room air. A thoracotomy was performed and the left anterior descending coronary artery occluded while electrocardiogram was continuously monitored and recorded. No significant difference was noted in death and incidence of VT following myocardial infarction in either control or hypertrophied groups. However, the duration of ventricular tachycardia was significantly prolonged in the hypertrophied group as well as the incidence of VF (91% vs 50%) ($p<0.05$). The number of VF events (8 ± 3 vs 2 ± 0.8) and the duration (51 ± 12 vs 30 ± 16 min) were greater in the hypertensive animals. These results reveal that a significantly higher incidence of VF in the hypertrophied group may represent a greater electrical instability associated with hypertrophy. This electrical instability may be the explanation for the higher incidence of sudden death in the hypertensive hypertrophied population.

THE RIGHT VENTRICLE (RV) IS THICKER IN HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY (LVH).
Boris Nunez, M.D., Franz H. Messerli, M.D., F.A.C.C., Celso Amodeo, M.D., Guiellermo Garavaglia, M.D., Roland Schmieder, M.D., and Edward D. Frohlich, M.D., F.A.C.C., Ochsner Clinic and Alton Ochsner Med. Fdn., New Orleans.

To assess RV changes in patients with essential hypertension (EH) electrocardiographic and M-mode echocardiographic criteria were used. 24 patients with uncomplicated essential hypertension were divided into two groups, those without LVH and those with LVH, and compared with 14 normotensive subjects (NT). Right and left ventricular dimensions and left atrial emptying index (LAEI) were (mean ± 1 SD):

	NT (n=14)	Without LVH (n=14)	With LVH (n=10)
MAP	96±7	116±6	115±8
RVWT(d)	3.8±.84mm	4.2±.57mm	7.3±1.8mm*
RVWT(s)	8.6±1.2mm	9.2±1.4*	13.3±3mm*
LAEI	.77±3.9	.40±1.2	.44±3.8*
LVM	82±20gr/m2	92±24gr/m2	100±35gr/m2
LVPW(d)	8.8±1mm	8.8±1mm	12.2±1mm
ST(d)	9.5±.9mm	9.6±9mm	17.5±.1mm

MAP=mean arterial pressure; LVM=LV mass; LVPW=LV posterior wall thickness; ST=septum; d=diastolic; s=systolic. Right ventricular wall thickness (RVWT) increased in patients with LVH when compared to those without LVH and normotensive subjects ($p<0.01$). LAEI was already diminished in patients without LVH as compared with the normals ($p<0.01$). We conclude that RV wall changes are associated with those of the left side and reflect a structural adaptation to increased afterload and/or other factors stimulating myocardial hypertrophy. The decrease in LAEI represent early diastolic functional changes associated with impaired ventricular compliance in the early process of LVH.

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DIFFERENCES IN GLOBAL AND REGIONAL LEFT VENTRICULAR PERFORMANCE IN HYPERTENSION AND AORTIC STENOSIS WITH NORMAL CORONARY ARTERIES

Charles K. Francis, M.D. F.A.C.C., Allan V.N. Goodyer, M.D. F.A.C.C., Robert Higgins, M.D., Michael Remetz, M.D., Yale University School of Medicine, New Haven, CT

Alterations in left ventricular performance which occur with pressure overload due to hypertension (HTN) may differ from changes associated with aortic stenosis. In 31 patients (pts) with normal coronary arteries, 17 with essential HTN and 14 with aortic stenosis (AS), regional wall motion (RWM) was assessed from contrast left ventriculography and compared to 25 normals (N), using a computerized technique in which RWM (mean percentage chord shortening) was calculated for 6 ventricular regions: anterobasal (AB), anteromedial (AM), anteroapical (AA), inferoapical (IA), inferomedial (IM), and inferobasal (IB). Global ejection fraction was above normal in HTN (77%, p <.02) but normal in AS (72%). RWM in HTN was significantly increased in the AM region (72 vs 58 (N)). In AS, RWM was significantly decreased in the IA (31 vs 41 (N)) and IM (28 vs 36 (N)) regions. These data indicate that pressure overload is associated with abnormalities in RWM in the absence of coronary artery disease. The pattern of these abnormalities in RWM may vary with the etiology of the increased pressure load, HTN demonstrating generalized hyperkinesis, greatest in the anteromedial region and AS showing hypokinesis in the inferoapical and inferomedial regions. These observations are important when evaluating RWM in pts with left ventricular pressure overload associated with other cardiac diseases.

IMPROVEMENT OF DIASTOLIC FILLING FOLLOWING HYPERTROPHY REVERSAL.

Julio F. Tubau, M.D., Jadwiga Szlachcic, M.D., Barry M. Massie, M.D., FACC, Steven Henderson, CNT, Carol Vollmer, R.N.; VA Medical Center and UCSF, San Francisco, California

Diastolic filling (DF) abnormalities are common in hypertensive (HTN) patients (PTS). Blood pressure (BP) control for up to 3 months in unselected HTN PTS has inconclusively affected DF. Therefore, we prospectively studied 18 HTN PTS with echocardiographic (ECHO) evidence of left ventricular hypertrophy using list mode radionuclide angiography (RN). PTS received either propranolol or labetalol with diuretic added if necessary to achieve BP control (diastolic BP $\leq$ 90 mmHg). ECHO left ventricular mass (LVM) and RN studies were performed after 4 weeks off therapy at baseline (B), and after 3, 6 and 12 months of BP control. RN studies were analyzed for ejection fraction (EF), end diastolic volume (V), peak filling rate (PFR), normalized first 1/3 filling fraction (NFF1/3) and atrial index (AI).LV mass was significantly reduced by treatment from 280±37 to 257±39, 249±29 and 251±30 gm and supine BP from 168±14/101±5 to 139±21/84±6, 139±20/83±6 and 134±20/81±9 mmHg at 3,6 and 12 months respectively (all p <.01 vs B).

	HR (bpm)	EF (%)	V (ml)	PFR (ml/sec)	NFF1/3 (%/sec)	AI (%)
B	65±10	65±7	122±17	2.5310.4	37±10	35±10
3m	60±7*	69±5*	128±17	2.89±0.5*	43±9*	32±7*
6m	60±7*	70±7*	120±22	2.80±0.5*	42±7*	33±5
12m	58±9*	69±10*	128±22	2.78±0.5*	44±10*	30±5*

*p<.01

Thus, following hypertrophy reversal DF improved by 3 months and was maintained for the remainder of the followup. However, the improvement was modest and DF did not achieve normal values, suggesting a nonreversible component of DF abnormalities in HTN.

Tuesday, March 11, 1986
4:00PM-5:30PM, Room #366/367
Clinical Hypertension

EPINEPHRINE FACILITATES NEUROGENIC VASOCONSTRICTION IN NORMAL AND BORDERLINE HYPERTENSIVE SUBJECTS.

John S. Floras, MD, Philip E. Aylward, MD, Ronald G. Victor, MD, Allyn L. Mark, MD, FACC, and Francois M. Abboud, MD, FACC, Cardiovascular Center, University of Iowa, Iowa City.

Epinephrine (EPI) augments neurogenic vasoconstriction most likely by facilitating the release of norepinephrine (NE) from sympathetic nerves both when blood levels are increased and as a co-transmitter released from adrenergic nerves when blood levels are baseline. To test the hypothesis that this effect of EPI on pre-junctional beta receptors is exaggerated in borderline hypertensives (BHT) we contrasted vasoconstrictor responses to a reflex stimulus (lower body negative pressure, LBNP) and to intra-arterial NE (18 ng/min) in age-matched subjects before, during and 30 min after infusion of EPI (50 ng/min) into a brachial artery. Forearm blood flow was measured simultaneously in both arms. The ratio of forearm vasoconstrictor responses (FVR) to LBNP/FVR to NE was used as an index of neurogenic vasoconstriction in these 3 periods. Results: Ratio of FVR LBNP/FVR NE (infused arm)

	Normal (n=8)	BHT (n=7)
Before EPI	1.5	0.8
During EPI	5.1	4.1
After EPI	5.3	2.0

The increased ratio of FVR to LBNP/FVR to NE from control both during and 30 min after infused EPI suggests that EPI facilitated neural NE release both directly and as a co-transmitter. Increases in this ratio from control during and after EPI did not differ significantly in the 2 groups. The results indicate that 1) EPI acts directly and as a cotransmitter to facilitate neurogenic vasoconstriction in humans and 2) this effect does not appear to be augmented in borderline hypertensive subjects.

PULMONARY VASCULAR HYPERSENSITIVITY TO ENDOGENOUS AND EXOGENOUS CATECHOLAMINES IN HYPERTENSION.

Maurizio D. Guazzi, M.D., Cesare Fiorentini, M.D., Paolo Moruzzi, M.D., Mauro Pepi, M.D., Gloria Tamborini, M.D.

Institute of Cardiology, C.N.R., University of Milan, Italy

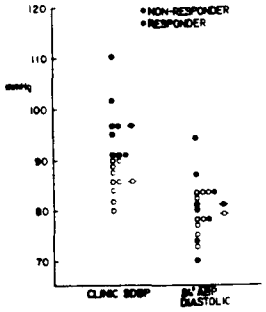
Elevated pulmonary pressure and resistance in mild uncomplicated hypertension suggests that a common mechanism may produce vasoconstriction in the greater and lesser circulations. This study was carried out in 16 such patients and in 9 healthy subjects to compare the vascular reactivity to release of endogenous catecholamines elicited by mental arithmetic (MA) and cold pressor test (CPT) and the dose-response relationship to exogenous (i.v.) epinephrine (Ep) and norepinephrine (NEp). MA and CPT were associated with a predominant rise of Ep and NEp, respectively. Changes were significantly greater in hypertensives (Ep during MA +62 pg.ml; NEp during CPT +65 pg.ml) than in normotensives (Ep during MA +10; NEp during CPT +11). During these stimuli pulmonary arteriolar resistance in normotensives was reduced by 13 % and augmented by 7 % of baseline, respectively; whereas in hypertensives it was raised by 31 and 70 %. In normotensivesthe dose (ug)-response (dynes) relationships to Ep and NEp were, respectively: 1=-4, 2=-5, 3=-8, 4=-10 and 2=+3, 4=+6, 6=+7, 8=+9. These relationships in hypertensives were: 1=+19, 2=+44, 3=+59, 4=+77 and 2=+39, 4=+45, 6=+76, 8=+104. Group differences were statistically highly significant. Cardiac output was raised by Ep and slightly reduced by NEp, both endogenous and exogenous. In each of these circumstances pressure in the pulmonary artery was significantly augmented in hypertensives and not in normotensives.

These findings document that in hypertension both catecholamines, from either source, have a pressor and vasoconstrictor effect in the lesser circulation as a consequence of vascular overreactivity. The opposite direction of changes in resistance between normotensives and hypertensives produced by Ep, suggests that a vasoconstrictor vascular oversensitivity becomes active in the pulmonary circuit with the development of systemic hypertension.

LIMITATIONS OF STANDARD CLINICAL TRIAL DESIGN IN ASSESSING ANTIHYPERTENSIVE DRUG RESPONSE. Alan H Gradman, MD, FACC, Michelle M Germain, BS, Patti A Pangan, BS, West Haven VAMC and Yale Univ, New Haven, CT.

We recently evaluated a new antihypertensive agent using both clinic and 24 hr. noninvasive ambulatory BP monitoring (ICR) to assess therapeutic efficacy. Fourteen male pts (mean age 59) were admitted to the study on the basis of a clinic supine diastolic BP (SDBP) during placebo of 95-115 mm Hg and then received either blinded placebo or one of three doses of an experimental agent. For dosage adjustment, pts were classed "responders" if the clinic SDBP was ≤ 90 mm Hg. A comparison of clinic and 24 hr ABPs in "responders" (n=9) and "non-responders" (n=8) was performed (n=17 dosage trials in 14 pts):

		"Non-Responders"	"Responders"	p
Clinic Supine	SBP	157 ± 15	139 ± 19	<05
	DBP	97 ± 7	86 ± 4	<001
24 mean	SBP	130 ± 14	128 ± 11	NS
	DBP	81 ± 7	79 ± 4	NS
Daytime ABP	SBP	133 ± 14	137 ± 12	NS
(8AM-4PM)	DBP	83 ± 7	85 ± 6	NS



Thus, "responders" and "non-responders" showed little difference in mean 24 hr or daytime systolic or diastolic BP, and 4/8 (50%) "non-responders" had a 24 hr DBP ≤ 80 mm Hg. These data suggest that clinic BP alone provides an incomplete view of drug response and is an imperfect guide to dose titration in hypertensive patients.

SERIAL ASSESSMENT OF RENAL PERFUSION IN EXPERIMENTAL RENOVASCULAR HYPERTENSION BY POSITRON TOMOGRAPHY WITH RB-82

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Renal perfusion was measured with positron tomography (PET) and a continuous infusion of the ultra-short half-life (75 sec) rubidium-82 (Rb-82) in experimental renovascular hypertension. Renal blood flow calculated from PET was compared to that determined by left atrial injection of microspheres. Renal perfusion images and microsphere injections were recorded in each 6 dogs at control, during renal artery stenosis and its occlusion. Renal concentrations of Rb-82 (Ct) were determined by PET and arterial activity (Ca) measured by well counting of blood samples. Ct/Ca was correlated with renal blood flow (F) measured by microsphere injected at each point, according to steady state compartment model.

$$Ct/Ca = 0.515 \times F / (0.195 \times F + \lambda) \quad r=0.85, (p<0.001)$$

(λ = decay constant)

Blood pressure was 113±17/76±18 at control, increased to 133±16/89±21 and 132±24/76±18 during stenosis and occlusion (p<0.001). The Rb-82 estimated flow was 2.8±0.6 ml/min/g at control, 1.2±0.8 ml/min/g during stenosis and 0.8±0.9 ml/min/g during occlusion. In addition, the contralateral kidney demonstrated flow reduction to mean 82% and 86% of the control values during stenosis and occlusion, respectively.
This data suggests that PET with Rb-82 permits repetitive quantitative assessment of renal perfusion noninvasively in acute renovascular hypertension.

CLONIDINE SUPRESSION TEST IN THE DIAGNOSIS AND POSTOPERATIVE CONTROL OF PHEOCHROMOCYTOMA

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In 8 patients (pts) with arterial hypertension pheochromocytoma was suspected because of symptoms and abnormally elevated urine and plasma catecholamines. From all pts blood was sampled in the supine position before, 120, and 180 minutes after 300 ug cloinidine (C) orally. Noradrenaline (NA) and adrenaline (A) was determined using a radioenzymatic method.

Results:		before		120 min		180 min	
				after clonidine			
	(pg/ml)	NA	A	NA	A	NA	A
1		362	30	251	108	211	89
2		479	11	70	75	131	11
3		340	41	119	71	201	39
4		715	92	442	65	353	51
5		363	41	110	12	97	12
6		423	100	109	25	184	23
7	preoperatively	3816	1975	4292	2158	3770	1821
	postoperatively	439	47	238	9	196	17
8	preoperatively	12239	34	12866	39	11183	18
	postoperatively	4220	66	3372	24	2290	18

Normal range: NA 219 ± 56 pg/ml
A 44 ± 28 pg/ml
mean value ± 2 SD

In 6 pts, in whom NA was outside the upper normal limit before C, it became normal after C. In all 6 pts the abdominal computed tomography (CT) was normal. In the 7th pt with highly elevated plasma catecholamines, not suppressible by C, CT revealed a left sided adrenal gland tumor. The diagnosis of pheochromocytoma was confirmed at surgery. In the 8th pt an extramedullary tumor could be identified by CT. Intraoperatively, a malignant pheochromocytoma was found with metastases located in the peritoneum and liver,which were missed by CT. Postoperatively, the C suppression test was repeated in both pts with pheochromocytoma. Whereas plasma catecholamines dropped to normal after C in the pt with a pheochromocytoma located in the adrenal gland, this was not the case in the other pt in whom metastases persisted after operation. – Conclusion: 1) C suppression test is a useful aid in the diagnosis of pheochromocytoma, especially in pts with arterial hypertension and elevated urine and plasma catecholamine concentration. 2) The C suppression test seems to be suitable to assess the efficacy of tumor resection.

RED BLOOD CELL (Na+K)ATPase IN NEWLY DIAGNOSED AND PREVIOUSLY TREATED ESSENTIAL HYPERTENSION

Richard Ringel, MD FACC, John Hamlyn, PhD, Gerard Pinkas, Bruce Hamilton, MD Univ. of Maryland, Baltimore.

In the presence of (Na+K)ATPase(Na pump) inhibitors, (eg. digoxin or hypokalemia) the hematopoetic system can increase the number of Na pumps/RBC, thereby "escaping" inhibition. Elevated levels of an endogenous Na pump inhibitor have been found in essential hypertension (EH). If this inhibitor is a natriuretic hormone, levels should decrease after blood pressure (BP) is lowered by diuretic therapy, allowing RBCs with fewer pumps to be formed. When therapy is discontinued, hypertension recurs and levels of circulating inhibitor rise. RBC Na content should then rise until new RBCs with more pumps can again be produced.

Therefore, RBC Na content, Na pump #/cell and activity were measured in black males with newly diagnosed EH (NEH,n=27) and with previously treated EH (PEH,n=21). Hypertension in PEH subjects was controlled with diuretics ± additional therapy in the preceding 6 mos but medications were discontinued 2-6 wks prior to study. Subjects were ≥ 30 yrs and had mean BP ≥ 108mmHg. Na content was measured by atomic absorption, Na pump # by ^{3}H-ouabain binding and pump activity by colorimetric methods. Data for the two groups included:

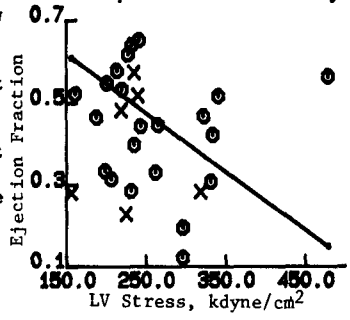
	RBC Na Content (mmole/l RBC)	*Na Pump# (#/RBC)*	*Na pump Activity (umolePi/mg protein/hr)*
NEH	*7.77 ± 2.53*	*284 ± 85*	*221 ± 87*
p=	*.006*	*.001*	*.03*
PEH	*10.27 ± 3.23*	*213 ± 40*	*166 ± 50*

In summary, our data show an elevated RBC Na content with reduced Na pump# (and activity) in PEH v NEH. These results support the hypothesis that in EH upregulation of RBC Na pumps develops in response to increased levels of a humoral (Na+K) ATPase inhibitor.

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #364/365
Valve Surgery: Hemodynamic Predictors and Outcomes

LOW WALL STRESS AND EJECTION FRACTION DO NOT PRECLUDE VALVE REPLACEMENT IN AORTIC STENOSIS WITH HEART FAILURE.
Mark L. Smucker, MD, FACC, David S. Knitter, BS, Charles L. Carman, ME, Thomas D. Stuckey, MD, Donald L. Tyson, BSN, Thomas W. Nygaard, MD, FACC, Irving L. Kron, MD, FACC, Robert M. Mentzer, MD, Robert S. Gibson, MD. University of Virginia, Charlottesville, Virginia.

Aortic valve replacement in patients with aortic stenosis is sometimes withheld due to severe left ventricular (LV) failure and previous findings that low ejection fraction and low transvalvular gradient in the face of low afterloading wall stress implies poor surgical outcome. Mean LV stress and ejection fraction at cath in 30 patients with severe aortic stenosis undergoing aortic valve replacement in 1983-4 are plotted below (X=dead, O=improved) along with previous authors' regression line for patients with good surgical outcome in the 1970's. Our patients with poor surgical outcome could not be separated from those with good outcome on the basis of wall stress and ejection fraction. In fact, most of our patients survived operation and improved dramatically despite falling well below previous authors' regression line. There were no deaths in patients without coronary disease. Our findings might be attributed to better current techniques of myocardial preservation. Aortic valve replacement is indicated in patients with aortic stenosis despite severe ventricular failure.



PREOPERATIVE NONINVASIVE END SYSTOLIC STRESS/END SYSTOLIC VOLUME RATIO IN MITRAL REGURGITATION: PREDICTOR OF POSTOPERATIVE SYMPTOMS.
Jessica Furer, M.D., David Pazer, B.S., Nathaniel Niles, M.D., Clare Hochreiter, M.D., Paul Kligfield, M.D., F.A.C.C., Richard Devereux, M.D., F.A.C.C., Jeffrey S. Borer, M.D., F.A.C.C., Cornell Medical Center, New York.

The ratio of LV end systolic stress to end systolic volume(ESS/ESV) has been proposed as a load independent contractility index in mitral regurgitation(MR) which might be useful in defining the timing of mitral valve replacement(MVR). When determined invasively, preop ESS/ESV has correlated well with post MVR course and function, but predictive power of non-invasive ESS/ESV measurement has not been assessed. Therefore, we obtained preop echocardiographic LV dimensions and simultaneous sphygmomanometric blood pressure for ESS/ESV determination in 15 pts undergoing MVR for isolated severe MR, and compared results to symptoms(Sx) and LV function determined by radionuclide cineangiography(RNCA) ejection fractions(EF) at av 11.9 mos postop. Nine of 11 patients with ESS/ESV>1.1 had no or minimal Sx postop (NYHA functional class[FC] 1 or 2), while 4/4 pts with ESS/ESV<1.1 had persistent FC≥3 Sx ($p<.025$). Predictive accuracy(PA) of ESS/ESV for such postop Sx was 87%. No other preop variable, including RNCA LVEF and RVEF (rest and exercise[ex], echo LV dimensions, and treadmill ex duration predicted postop Sx, regardless of cutpoint chosen. In addition, pts with preop ESS/ESV <1.1 trended to lower postop $LVEF_{rest}$ (37% vs 45%,NS) and ex (38% vs 46.5%,NS) and less ex tolerance (6±2 min vs 8±3 min,NS) than pts with preop ESS/ESV>1.1. Noninvasive echocardiographic ESS/ESV ratio may be of value in defining optimal timing of MVR in pts with MR.

FAILURE OF HEMODYNAMIC-ANGIOGRAPHIC MEASURES TO PREDICT OUTCOME IN REGURGITANT VALVULAR HEART DISEASE.
Marc C. Cohen, M.D., William G. Kussmaul, M.D., Joseph P. Kleaveland, M.D., F.A.C.C., John W. Hirshfeld, Jr., M.D., F.A.C.C., Warren K. Laskey, M.D., F.A.C.C., University of Pennsylvania, Philadelphia, PA.

The peak LV systolic pressure: end-systolic volume ratio (P/V), an approximation of the end-systolic pressure-volume relationship, has been reported to be a sensitive index of LV disease. We determined P/V at cardiac catheterization in 36 patients (27 operated upon) with chronic mitral regurgitation and 30 patients (16 operated upon) with chronic aortic regurgitation to assess the relationship between P/V and survival, overall outcome (no need for surgery or post-operative improvement versus poor operative outcome), and post-operative improvement. In addition, the following variables were evaluated to determine if they were associated with survival, overall outcome, and post-operative improvement: pulmonary wedge pressure, LV end-diastolic pressure, CO, ejection fraction, end-systolic volume, and end-systolic volume index. P/V was not associated with survival, overall outcome, or post-operative improvement in either aortic or mitral regurgitation. In aortic regurgitation, ejection fraction was the only variable associated with survival (60%±8.5 vs. 40%±12.9, $p=.002$), overall outcome (60%±8.6 vs. 43%±14, $p=.001$), and post-operative improvement (55%±5 vs. 44%±15.7, $p=.05$). We conclude: 1)P/V is not associated with survival, overall outcome, or post-operative improvement in patients with aortic or mitral regurgitation; 2)In aortic regurgitation, ejection fraction is associated with all 3 endpoints.

VALUE OF THE REGURGITANT VOLUME TO END-DIASTOLIC VOLUME RATIO IN THE EVALUATION OF PATIENTS WITH AORTIC REGURGITATION
Patrick T. O'Gara, MD, Robert O. Bonow, MD, FACC, Gale G. White, RN, Barry J. Maron, MD, FACC, Steven L. Bacharach, PhD and Michael V. Green, MS, NHLBI, Bethesda, Md.

Preoperative LV systolic function is an important determinant of survival and functional results following aortic valve replacement (AVR) for chronic aortic regurgitation (AR). However, many pts with pre-op LV dysfunction manifest improved LV function after AVR and have an excellent prognosis. To test the hypothesis that the magnitude of regurgitant volume (RV) relative to end-diastolic volume (EDV) may predict the post-op outcome in such pts with AR, we used radionuclide angiography to study 59 pts (ages 19-72, mean 44): 22 pts with normal pre-op LV ejection fraction (EF) and 37 pts with subnormal pre-op LVEF. In pts with normal LVEF, the RV/EDV ratio was significantly related to the pre-op LV diastolic dimension (DD) index ($r=.70$, $p<.001$) and predictive of the change in DD that occurred after AVR ($r=.70$, $p<.001$). In pts with subnormal LVEF, no such correlations were found, presumably because LV dilatation in some pts exceeds that which is appropriate for the regurgitant volume alone and, therefore, reflects irreversible dysfunction. However, among pts with subnormal pre-op LVEF, the pre-op RV/EDV ratio did distinguish between groups at high and at low risk of death and/or post-op heart failure (CHF). Of those 16 pts with an RV/EDV ratio >0.25, there was only 1 death and no post-op CHF, whereas among the 21 pts with an RV/EDV ratio ≤0.25, 7 pts died and 3 had post-op CHF ($p<.01$). Thus, the RV/EDV ratio is not predictive of the change in LV size following AVR in pts with subnormal pre-op LVEF, but may provide additional prognostic information regarding survival and clinical outcome in this group.

EFFECTS OF SEVERITY AND TYPE OF OVERLOAD ON MYOCARDIAL BLOOD FLOW RESERVE IN EXPERIMENTAL AORTIC VALVE DISEASE.
Alfred A. Bove, M.D., F.A.C.C., Qian Sufan, M.D., Jose M. Brum, M.D., Mayo Clinic, Rochester, Minnesota.

In this study we hypothesized that myocardial blood flow reserve (BFR) is reduced in proportion to the degree of hypertrophy in aortic stenosis (AS) and in aortic insufficiency (AI). We created pure valvular AS in 6 dogs, AI with mild stenosis in 5 dogs, and sham operated 7 dogs (S). BFR was measured with radioactive microspheres at rest, during intracoronary adenosine (ADO) infusion (1 mg/min), and with pacing induced tachycardia. Left ventricular (LV) performance was determined by computer analyzed, 30/sec biplane ventriculograms. A systolic aortic valve gradient was present in AS (57±27 mmHg) and AI (34±10). In AI total LV output was 2.2 times forward cardiac output. End diastolic volume was increased ($p<.05$) in AI (96±21 ml) compared to AS (73±8) and sham (61±9), and LV mass was highest ($p<.05$) in AI (7.2±.4 g/kg) compared to AS (6.4±.9) and sham (4.8±.5). LV mechanical work output (W) was highest ($p<.05$) in AI (170±34 Joules/min) compared to AS (66±10) and sham (57±14), and LV mass was correlated with W ($R = .516$, $p<.05$). BFR expressed as peak/resting flow comparing ADO flow with control was inversly correlated with LV mass ($R = .638$, $p<.02$) across a spectrum of severity of AS and AI, and fits a curvilinear function which assumes no vasogenesis with hypertrophy. We conclude: 1) LV mass is proportional to LV power requirements in both AS and AI; 2) increasing mass produces a loss of BFR; and 3) reduced BFR follows a relationship which indicates that vasogenesis does not occur in the adult heart subject to hypertrophy from aortic valve disease.

CORRELATION OF PHYSICAL FINDINGS IN AORTIC INSUFFICIENCY WITH HEMODYNAMIC SEVERITY.
MD Cheitlin, MD, FACC; JD Bristow, MD, FACC; B Massie, MD, FACC; B Greenberg, MD, FACC; D Thomas, PhD, G Krishnamurthy MD; D Loge, BS, N Topic, RN; D Siemienczuk, RN; J Newlands, BA; University of California, San Francisco.

85 patients (pts) (35 UCSF, 47 Oregon Health Sciences University) with varying degrees of aortic insufficiency (AI) had physical findings (PF) correlated with objective measures of hemodynamic severity (HS) determined by radioisotope blood pool studies of LV end diastolic volume index (EDVI), end systolic volume index (ESVI), regurgitant fraction (RF), and total LV stroke volume (SV).

Significance of Correlation (p value) NS=not significant

Physical Findings	EDVI	ESVI	SV	RF
Systolic BP	NS	NS	NS	NS
Diastolic (D) BP	.0004	NS	.0001	.0008
Pulse pressure	.04	NS	NS	NS
Duration Diastolic Murmur (DM)	.002	.04	.002	NS
Grade DM	.0005	NS	.00001	NS
Summary Peripheral Signs of AI	.0009	.02	.002	NS

		Absent	Present	Sig
Austin-Flint M	EDVI	137.0±43.1	165.6±48.0	.007
(vol. = cc	LVSV	91.1±37.4	109.8±28.1	.005
± 1 S.D.)	RF (%)	58.5±48.01	67.9±14.0	.005
S_3	RF (%)	56.4±12.7	70.5±9.1	.001
Quinke's	EF (%)	63.5±8.1	67.7±9.3	.04
Duroziez' M*	EDVI	107.1±22.6	147.5±36.6	.0001
Water Hammer Pulse	NS correlations		*UCSF only, N=38	

There were marked differences in incidence of several PF in pts from UCSF and OHSU, i.e., S_3 in UCSF pts in 13/38 and OHSU in 1/46, and Duroziez' M in 18/36 UCSF and 4/46 OHSU pts. The most helpful PF correlating with HS are D BP, duration and grade of DM, presence of Austin-Flint M, S_3, and overall summary of PF of AI.

Tuesday, March 11, 1986
4:00PM–5:30PM, Room #364/365
Myocardial Infarction—Clinical: Metabolic Changes

PREDICTION OF INFARCT SIZE FROM CARDIAC MYOSIN LIGHT CHAINS SERUM LEVELS.
Peter P. Liu, M.D., Tsunehiro Yasuda, M.D., F.A.C.C., H. William Strauss, M.D., F.A.C.C., Herman Gold, M.D., F.A.C.C., Edgar Haber, M.D., F.A.C.C., Ban-An Khaw, Ph.D. Massachusetts General Hospital, Boston, MA.

The soluble light chains fraction (LC) of cardiac myosin can be detected in serum after myocardial infarction (MI) using a radioimmunoassay (RIA) technique. It has been shown to be an early and sensitive marker of myocardial necrosis. To determine the potential relationship between the amount of LC release to infarction size (IS), we obtained serial serum samples from 18 acute MI patients at 6 hourly intervals for up to 6 days, and quantitated the LC levels with liquid-phase RIA. The area under the LC concentration-time curve was also integrated from time 0 to each of 24, 72 and 120 hrs following admission. To determine infarct size, patients were injected intravenously with Tc-99m labelled antimyosin Fab antibody, and the volume of uptake from the reconstructed single photon emission tomographic slices was converted to gram-equivalent of infarct tissue. Linear regression analysis was performed between both the LC level (ng/ml) and LC area integral (ng/ml-hr) with infarct size (gm) at different time intervals, and the correlation coefficients (R) are as follows:

Time after admission	0 hr	24 hr	72 hr	120 hr
LC concentration(ng/ml)*	31±33	45±30	58±38	48±30
R (LC vs IS)		0.88**	0.71	0.71
R (LC integral vs IS)		0.83	0.79	0.83

**multiple regression identified a single 24hr LC level to correlate the best with IS ($y=.86x+11$; $p<.001$). * mean±SD

Conclusion: Myosin light chains are released early after MI and usually persist for more than 6 days in the serum. A single level taken at 24 hrs correlates well with myocardial infarction size. Therefore RIA of serum LC may be used to predict the size of myocardial necrosis from a single 24 hr sample.

PROMPT DETECTION OF ACUTE MYOCARDIAL INFARCTION BY ANALYSIS OF CK ISOFORMS IN THE FIRST AVAILABLE BLOOD SAMPLE.
Allan S. Jaffe, M.D., F.A.C.C., Ann Grace, and Burton E. Sobel, M.D., F.A.C.C., Washington University, St. Louis, MO.

Acute myocardial infarction often can not be detected as promptly as desired with conventional plasma isoenzyme and enzyme assays because most molecular markers of myocardial injury are liberated slowly. However, we have previously detected infarction within 1 hr after coronary occlusion in dogs by exploiting the rapid post-translational modification of the myocardial MM CK (MM_A) isoform that gives rise to different isoforms of MM CK (MM_B and MM_C) in plasma. To determine whether infarction can be detected promptly in patients as well, we assayed MM CK isoforms with an immunoblot procedure in the first available plasma samples from 12 patients with chest pain suggestive of infarction and 14 normal controls. In each control subject and patient MB and total CK values were well within the normal range in the same samples as those used for isoform analysis. Total and MB CK values were virtually identical in patients compared with controls (92 ± 30 [SD] IU/l and 94 ± 33; 5.2 ± 2 and 5.0 ± 3). However, the fraction of MM CK attributable to the MM_A compared with the MM_C isoform in plasma was markedly different. For controls it averaged 1.3 ± .66 and did not exceed 2.4. In contrast, even though total and MB CK values were normal, corresponding ratios of MM_A/MM_C in the first available sample from patients with evolving infarction averaged 16. The ratio exceeded 2.6 (mean + 2 SD in controls) in 75%. Thus, assay of MM CK isoenzymes in the first available blood sample permits early detection of myocardial infarction well before MB CK and total CK values exceed the normal range.

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DECREASED SERUM LEVELS OF PGI_2 STABILIZING FACTOR AND PGI_2 SYNTHESIS STIMULATING FACTOR IN ACUTE MYOCARDIAL INFARCTION

T.Aoyama, MD, Y.Yui, MD, Y.Takatsu, MD, R.Hattori, MD, T.Susawa, MD, N.Ikeda, MD, K.Sakaguchi, MD, M.Takahashi, MD, C.Kawai, MD, FACC, Kyoto University, Kyoto, Japan.

Human serum is known to contain two important factors which regulate PGI_2 metabolism. This study was aimed to investigate the possible role of these factors in the pathogenesis of acute myocardial infarction(AMI). The one factor stimulates PGI_2 synthesis in blood vessel. The aortic ring(2 mm length) of rat was incubated for one hour with 200 µl serum. The activity of this stimulating factor(SF) was expressed as 6-keto-$PGF_{1\alpha}$ ng/mg wet weight of the ring/hour. The other is stabilizing factor(STF) that binds to PGI_2. After incubation with [^{3}H]PGI_2 at 22°C for 3 minutes, one ml of serum was mounted on Sephadex G-25 column. A part of the activity of [^{3}H] was found at the voiding fraction corresponding to PGI_2-STF complex. The percentage of this activity for total activity was obtained and defined as the activity of STF. The activities of the two factors were determined in 7 patients with AMI 2.5±0.8(I) and 80±17(II) hours after the onset of chest pain, and compared with those obtained from 7 normal volunteers. Values are mean±SD.

	SF	STF
Volunteer	117±48	72±5.5
AMI (I)	15±15*	52±6.9*
AMI (II)	68±20*	63±5.5*

*p<0.05:Multiple comparison test was used for statistics.

In the very early phase of AMI the serum levels of SF and STF were significantly reduced, which may be related to the thrombus formation in the coronary artery in AMI.

INCREASED PLATELET AGGREGABILITY AFTER ARISING FROM SLEEP

Geoffrey H. Tofler, MBBS, Charles A. Czeisler PhD, MD, ACP, John Rutherford MB, FACC, Gordon H. Williams MD, James E. Muller MD, FACC Brigham and Women's Hospital, Harvard Medical School, Boston, MA

The frequency of onset of myocardial infarction (MI) has a marked circadian variation; the frequency of onset is low during sleep but rises sharply on awakening reaching a peak at 9 a.m. Since MI results from thrombus formation, we studied platelet aggregability during the transition from sleep to wakefulness and activity.

Seven normal male subjects were studied. Plasma norepinephrine (NE) and epinephrine (Epi), the mean concentration (conc) of ADP and Epi required to induce biphasic platelet aggregation in vitro, and the percent aggregation at threshold concentration (agg) were determined in two blood samples drawn prior to arising (6:30 and 8:00 a.m.) at which mean NE was 120 ± 29 pg/ml and Epi was 25 ± 3 pg/ml and in two samples drawn after waking and arising to normal activity (9:30 and 11:00 a.m.)at which mean NE was 310 ± 28 pg/ml and Epi was 57 ± 6 pg/ml. Mean values and standard error before and after arising were: (* $p < 0.05$)

	ADP (µM) agg.conc.	Epi (µM) agg.conc.	ADP %agg.	Epi %agg.
Prior to arising	2.8 ±0.2	1.6 ±0.3	24 ±14	12 ±17
After arising	2.2 ±0.2*	0.8 ±0.3	43 ±14*	37 ±17*

Thus, platelet aggregability is significantly increased after arising. Further study of this phenomenon could perhaps clarify the mechanism by which anti-platelet agents prevent MI and facilitate development of new interventions to prevent arterial thrombosis.

THE PROGNOSTIC IMPLICATIONS OF ELEVATED FIBRIN SPECIFIC CROSS LINKED PRODUCTS AFTER INFARCTION - A MARKER OF INTENSE ENDOGENOUS THROMBOSIS AND THROMBOLYSIS.

Paul R. Eisenberg, M.D., Burton E. Sobel, M.D., F.A.C.C., Laurence Sherman, M.D., Julio Perez, M.D., and Allan S. Jaffe, M.D., F.A.C.C., Washington University, St. Louis, MO.

We have previously documented thrombosis in vivo early after the onset of infarction by assay of fibrinopeptide A (FPA) in plasma. Assuming that intense and persistent thrombosis predisposing to complicated infarcts would be reflected by concomitant endogenous thrombolysis and hence production of cross linked fibrin degradation products (D-dimers), in the present study we assayed plasma D-dimer with an ELISA procedure. Plasma samples were obtained within 10 hr of the onset of pain in 65 patients with acute transmural infarction in whom mural thrombi had been excluded echocardiographically. As anticipated, FPA was elevated in 92% (33.5 ± 8.5 [SE] ng/ml, upper limit of normal = 2.0 ng/ml). D-dimer was normal (< 200 ng/ml) in 55% (138 ± 8 ng/ml), modestly elevated (< 400 ng/ml) in 17 % averaging 261 ± 16 ng/ml, and markedly elevated in 28% (2618 ± 838 ng/ml). Marked elevations of D-dimer portended severe congestive heart failure, ventricular fibrillation, or ventricular tachycardia within the first few hours. Thus, among the 18 patients with marked elevations, 10 (56%) had major complications of infarction. In contrast, among patients without marked elevations, such complications were rare (11%). These results indicate that early elevation of D-dimer indicative of ongoing, intense thrombosis and compensatory thrombolysis in vivo presage extensive and clinically complicated infarction.

ALTERED PLATELET ALPHA2-ADRENOCEPTOR IN ACUTE MYOCARDIAL INFARCTION AND ITS RELATION TO PLASMA CATECHOLAMINE LEVELS

K. Sakaguchi, R. Hattori, Y. Yui, Y. Takatsu, T. Susawa, N. Ikeda, S. Tamaki, H. Nonogi, C. Kawai. F.A.C.C.
Kyoto University, Kyoto, Japan.

To evaluate the down-regulation mechanism of platelet alpha2-adrenoceptor in acute myocardial infarction(AMI), we studied the changes of the receptor and its relation to plasma epinephrine(E) and norepinephrine(N) levels. Alpha2-adrenoceptor of platelet membrane was studied using [^{3}H]-yohimbine and E & N were analyzed by high-performance liquid chromatography. The number of alpha2-adrenoceptor(Bmax), the dissociation constant (Kd), and E & N were compared between 6.6±3.3 hours after the onset of AMI and one month later in 11 patients with AMI; Bmax increased significantly from 96.5±50.5 to 157.0±65.7 fmoles/mg protein($p<0.01$). However, Kd did not change significantly(4.33±1.40 vs 4.37±1.22 nM) E & N, 51±25 & 946±739 pg/ml were normalized to 16±9 & 206±114pg/ml, respectively($p<0.05$ for both).

Although the down-regulation mechanism of platelet alpha2-adrenoceptor is still controversial, the above results suggest that the down-regulation mechanism may exist between the number of platelet alpha2-adrenoceptor and plasma catecholamine levels in AMI.

Tuesday, March 11, 1986
2:00PM-3:30PM, Room #157
Pediatric Interventional Cardiac Catheterization

BLADE AND BALLOON ATRIAL SEPTOSTOMY AFTER TRANSSEPTAL ATRIAL PUNCTURE

G. Wesley Vick, III, MD, PhD, Charles E. Mullins, MD, FACC, Michael R. Nihill, MD, FACC, J. Timothy Bricker, MD. Section of Cardiology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas.

Blade and balloon atrial septostomy (BBAS) has usually been performed by pulling the blade catheter through a preexisting atrial opening. We have expanded this technique and now, in selected cases, place the blade catheter across the interatrial septum through a sheath introduced after atrial transseptal puncture. Fourty-one of 88 BBAS procedures performed by us have employed this method. Primary diagnoses included transposition (Group I, n=16), left atrioventricular valve atresia or severe stenosis, (Group II, n=12), double outlet right ventricle with restrictive ventricular septal defect (Group III, n=2) tricuspid and/or pulmonary atresia (Group IV, n=6), and pulmonary vascular obstructive disease (Group V, n=5). Ages ranged from 1 day to 21 yrs (mean = 2.8 yrs) and weights from 3.5 to 65 kgs (mean 12.8 kg). Eighteen pts had an intact atrial septum prior to the procedure (7, Group I; 4, Group II; 2, Group III; 5, Group V). In 23 pts, a restrictive natural ASD was present initially and a second defect was created alongside it with the blade. Adequate enlargement of the natural ASD was not possible in these cases either because of unusual location, or because of blade slippage. There were two deaths, both in critically ill infants. Clinical improvement, sometimes dramatic, occurred in 36 pts. Improvement in groups IV and V was characterized by an increase in systemic perfusion and decrease in right-sided congestion. Improvement in groups II and III was associated with a decrease in pulmonary congestion (mean left atrial to right atrial gradient drop was from 17 to 4 mm Hg). Improved pts in Group I showed substantial increases in oxygen saturation (mean femoral arterial saturation increased from 62% to 73%). Thus the technique of transseptal puncture substantially extends the applicability and efficacy of BBAS.

PATHOLOGIC SEQUELAE OF BALLOON DILATION ANGIOPLASTY FOR UNOPERATED COARCTATION OF THE AORTA IN CHILDREN.

William J. Marvin, MD, FACC, Larry T. Mahoney, MD, FACC, Earl F. Rose, MD, University of Iowa, Iowa City, Iowa.

Vascular injury following balloon dilation angioplasty (BDA) has been described in coronary, pulmonary, and peripheral systemic arteries. After entry in an institutionally reviewed prospective protocol, eleven asymptomatic children (4-6 yrs) underwent BDA to treat unoperated coarctation (CA) of the aorta. Follow-up angiography revealed aortic aneurysms (AN) 7-14 mos. after BDA in six of these eleven patients. We report the pathologic findings in these six patients after surgery.

The adventitia was intact in all specimens. A single AN was found on either the greater or lesser aortic curvature in 5; one specimen had 2 AN. The AN ranged in size from 20-50% of the total aortic circumference. All former CA sites were torn linearly, but linear tears were also present proximally (2) and distally (4) to the CA in normal aortic media. No dissections or mural thrombi were associated with either the AN or the linear tears. Microscopically, each AN wall was markedly attenuated with almost a complete absence of vascular muscle and a variable loss of elastic lamella. In two specimens, occlusive neofibroelastic proliferation developed in juxtaposition to a linear tear, and distal to the former CA. Preexistant CA tissue and secondary intimal fibrosis were identified and distinct from this neofibroelastic proliferation.

Despite the early safety and efficacy of BDA in relieving hypertension and CA obstruction, the persistence of aortic tears and the development of both AN and obstructive neofibroelastic proliferation may compromise the eventual success compared to CA surgery. Whether these lesions will appear later in other patients is unknown and continual reevaluation is indicated.

BALLOON DILATATION IN INFANTS AND CHILDREN WITH VALVAR AORTIC STENOSIS.

M Choy, MD, RH Beekman, MD, FACC, DC Crowley, MD, AP Rocchini, MD. C.S. Mott Children's Hospital, University of Michigan, Ann Arbor

We evaluated the efficacy of balloon dilatation (BD) in 1 infant and 4 children with valvar aortic stenosis (AS) ages 7 months to 14 years. The infant had critical AS and was in severe congestive failure, and 2 of the 4 children had a previous aortic valvotomy. All patients were heparinized prior to angioplasty. The aortic valve gradient was determined using simultaneous LV and AO pressure measurements. The peak systolic ejection gradient (PSEG) across the aortic valve, LV and AO cineangiograms and cardiac indexes (CI) were obtained before and after the BD. The BD was performed in each patient using a balloon diameter (7 to 18 mm) that was 1 to 3 mm smaller than the aortic annulus diameter. LV pressure decreased from 178±9 to 150±8 mmHg ($p<.05$) (mean±SEM) and PSEG decreased from 77±14 to 37±5 mmHg ($p<.05$). Although there were no significant changes in HR (96±10 to 99±10) or CI (3.3± .3 to 3.3±.3 l/min/m^2), in the infant with critical AS the CI increased from 2.4 to 3.3 and mixed venous saturation increased from 52 to 65%. There were no complications during the procedures. Moderate AI was present in 2 patients following BD: one had mild AI prior to BD, and one (our first patient) underwent BD with a balloon size only 1 mm smaller than the annulus diameter. These data indicate that BD is a safe and effective means of treating valvar AS, even in infants and post operative patients. In addition, a balloon 2-3 mm smaller than AO annulus size should be used to minimize the development of AI.

BALLOON DILATION ANGIOPLASTY OF POSTOPERATIVE AORTIC OBSTRUCTIONS.

J Phillip Saul MD, John F Keane MD, Kenneth E Fellows MD, James E Lock MD FACC. Department of Cardiology, Children's Hospital, Boston MA

Eighteen patients(3months-22years) with significant postoperative aortic obstructions (gradient > 20mmHg) underwent balloon dilation angioplasty(BDA). Aortic obstructions followed subclavian flap repair(SCF) for coarctation(n=6), end-to-end(E-E) anastomoses for coarctation(n=5), patch angioplasty(PA) for coarctation(n=2), E-E anastomoses for interrupted aortic arch(IAA, n=4) and PA for hypoplastic left heart(n=1). One pt with E-E anastomoses for IAA had 3 sites of aortic narrowing postop, including 1 at the aortic bypass cannulation site; thus a total of 20 obstructions were dilated. Balloon sizes were chosen to be 2.5-3.0 times the diameter of the narrowing: in 4 patients the first balloon was too small, and a larger balloon (up to 4 times the diameter of the narrowing) was needed.

BDA was successful (>50%decrease in gradient) in 18 of 20 obstructions and 16 of 18 patients: 6/6 postop SCF, 4/5 postop E-E for coarctation, 2/2 postop PA for coarctation, 5/6 postop anastomosis obstructions (4 pts) for IAA, and 1/1 postop PA for hypoplastic left heart. Aortic obstructions increased in diameter post-BDA from 3.8± 2.3 mm to 6.9± 3.6 mm ($p<0.01$). Gradients across the obstruction decreased from 41±14mmHg to 11±8mmHg ($p<0.01$). In the child with multiple postop IAA obstructions, the total aortic gradient fell from 170mmHg to 35mmHg. Complications were few; post-BDA pulse loss was successfully treated with heparin/streptokinase. Followup (2-12mos) shows sustained relief in 8/9. Late angiography(n=4) revealed no aneurysms.

Previous reports have indicated that aortic obstructions following SCF or E-E anastomosis for coarctation can be relieved in most cases with BDA; these data further indicate that BDA provides significant gradient and anatomic improvement in most forms of postop aortic obstructions.

BALLOON VALVULOPLASTY FOR VALVAR PULMONARY STENOSIS USING OVERSIZED BALLOONS. Wolfgang Radtke MD, John F Keane MD, Kenneth E Fellows MD, Peter Lang MD, James E Lock MD FACC. Department of Cardiology, Children's Hospital, Boston MA.

The optimum balloon size for safe and effective dilation of valvar pulmonary stenosis(PS) is unknown. Although animal studies showed that the use of balloon diameters 20-50% larger than the valve annulus is safe, its safety and efficacy in children with PS has not been evaluated.

In 18 pts (6day-19yrs) with typical valvar PS, percutaneous balloon valvuloplasty(BV) was attempted using balloon diameters 0-65% (m=36%)larger than the angiographically determined annulus size(corrected for X-ray magnification). A twin balloon technique was employed in 3 pts; in those, the cross sectional area of the oval enveloping the two balloons was calculated; the diameter of a circle with an area equal to this oval was taken as the effective dilating diameter. Two pts had had previous surgical valvotomies; two others had had previous BV at other institutions.

Significant reduction of transvalvar gradient (33-100%, m=72%) occurred in each patient. The mean pre-BV gradient of 64mmHg (25-120mmHg) was reduced to 17mmHg (0-30mmHg). The calculated valve areas increased by an average of 180%. No significant pulmonary regurgitation was noted, and no complications occurred.

Two groups (Kan et al. and Rocchini et al.) have previously reported series of BV in PS giving actual balloon diameters (designed to be at or near annulus size). In those reports, mean patient age (4.8 yrs) was similar to ours (5.0 yrs); the average balloon size in those series (13.6mm) was smaller than our average balloon size(18.0mm). Despite similar predilation gradients, the gradient reduction using larger balloons was somewhar greater(72 vs 58%)*.

These data suggest that BV in PS with balloons 30-40% larger than the annulus is safe, and may result in improved gradient reduction.

*$p < 0.05$

BALLOON DILATATION OF SHUNT-RELATED PULMONARY ARTERY STENOSES AFTER TETRALOGY OF FALLOT REPAIR: EARLY AND SHORT TERM RESULTS. Guillermo R. Sanchez, MD, A.V. Mehta, MD, S.E. Brickley, CCPT, I.F.S. Black, MD, St. Christopher's Hospital for Children and Temple U. School of Medicine, Phila., PA.

Pulmonary artery stenoses (PAS) in pts with TOF complicate the long term course and may not be surgically correctable. We attempted balloon dilatation (BD) of 8 PAS [5 in RPA (4 at Waterston, 1 at BT); 3 in proximal LPA (1 at/near Gortex shunt)] in 5 pts after TOF repair. Balloon diameter was 2-5x RPA and 2-3x LPA stenoses diameter. Inflation pressure was 59-103 (RPA) and 66-88 (LPA) psi. BD result was assessed by pressure and cardiac output measurement, angiography, and radionuclide study. BD of LPA produced improvement in 1 pt (RV pre: 160, post: 105 mmHg; sustained over 6 mo) but not in 2 pts (despite increase in LPA size from 6 to 10 mm in 1 pt s/p Gortex). BD of RPA in 1 pt s/p Waterston (pt A) increased RPA size from 4 to 14 mm but produced little improvement in pulmonary flow pattern or RV pressure, related hemodynamically to the size of the non-stenotic proximal RPA, in 2 pts (s/p Waterston) produced no improvement in RV pressure despite small increase in RPA size, and in 2 pts (s/p Waterston, s/p BT) failed to obliterate the waist (at inflation pressures of 103 and 66 psi). No early complications occurred. Follow-up catheterization in pt A shows restenosis at previous site (RPA 8 mm) 5 mo after BD and in a second patient (s/p Waterston) shows perfusion deficits in the right lung 6 mo after angioplasty.

We conclude: 1. RPA stenosis at previous shunt is often poorly compliant, 2. increase in PA size after BD is not always accompanied by improved RV pressure (and thus may not be clinically significant) and may regress, 3) follow up studies after apparently successful BD of PAS are necessary.

Tuesday, March 11, 1986
4:00PM–5:30PM, Room #157
Pediatric Cardiac Electrophysiology

QT INTERVAL AND THE SUDDEN INFANT DEATH SYNDROME. A PROSPECTIVE STUDY.

Alessandro Segantini,M.D., Tiziana Varisco,M.D., Emanuela Monza,M.D., Valeria Songa ,M.D., Massimo Montemerlo,M.D., Patrizia Salice,M.D., Gianluigi Poggio,M.D., Dario Rosti, M.D., Peter J.Schwartz,M.D.,F.A.C.C.
Istituto Clin. Med. IV, Università di Milano, Italy

In 1976 we proposed that part of the Sudden Infant Death Syndrome (SIDS) may be due to ventricular fibrillation triggered by increased sympathetic activity. Decreased cardiac electrical stability would be enhanced by a transient developmental imbalance in cardiac sympathetic innervation. Prolongation of the QT interval is one of the markers of such an imbalance. Over 9500 non-consecutive newborns entered a prospective study started in 1977 and had an ECG taken on 4th day of life. One year survival data are now available for 6000 infants. There have been 6 SIDS and 4 non SIDS deaths. From our data base, QTc values > 433 msec exceed the mean by more than 2 standard deviations (397+18, $\bar{x}$+1SD) and are considered prolonged.

non SIDS (n=4) - QTc: 363,400,401,406
SIDS (n=6) - QTc: 440,440,451,460,480,563

Given the number of newborns with a QTc>433, our data suggest that the risk for SIDS, associated with a prolonged QT is approximately 40/1000 live births. Although more data on SIDS victims are still necessary, even a conservative analysis indicates that at least some of the future SIDS victims can be expected to have a prolonged QT interval. This may allow early identification of some infants at high risk for SIDS.

THE PERMANENT FORM OF JUNCTIONAL RECIPROCATING TACHYCARDIA: A CAUSE FOR CHRONIC SUPRAVENTRICULAR TACHYCARDIA IN CHILDREN.

Richard T. Smith, Jr., MD, Kim D. Armstrong, RN, Janette Strasburger, MD, Jeffrey P. Moak, MD, Arthur Garson, Jr., MD, FACC.

Chronic "incessant" supraventricular tachycardia (SVT) has most frequently been considered to be due to an atrial ectopic focus (AET). We report 22 cases of chronic reentrant SVT due to the permanent form of junctional reciprocating tachycardia (PJRT). Differentiation of PJRT from AET is possible by their characteristics and important because treatment differs. PJRT criteria were: 1) "Incessant" SVT present greater than 10% of a 24 hour period, 2) Visible P waves during SVT, negative in the inferior leads, 3) Normal or near normal PR interval during SVT, 4) Lack of "warm-up" at SVT onset, 5) Electrophysiologic study supporting a reentrant mechanism. Mean age at diagnosis was 3.9 yrs (range-fetal to 16 yrs). SVT rate on initial ECG ranged from 125 to 230 with a mean of 167. In each pt marked SVT rate variation occurred throughout a 24 hr period; 34 to 125 bpm (Max. minus Min. rate). Myocardial dysfunction (MD) was documented in 11/22 (50%). To detect differences between pts with MD and without, we compared the 2 groups. There was a tendency toward MD with higher rates, greater daily frequency and longer duration since diagnosis. The groups significantly differed when the 3 factors were combined. The pts received an average of 3.8 drugs; a traditional drug was effective in only 1/22 (verapamil). The investigational agent, encainide, completely suppressed SVT in 5/9 pts and improved control in the other 4. Catheter ablation improved SVT in 4 pts, however 3 required permanent pacing and 3 received adjunctive medication. SVT was successfully treated surgically in 4/4 pts; 2 had dissection of the posterior septum and developed AV block. The most recent 2 pts had cryoablation of the posterior septum and are cured of SVT with normal AV conduction. We conclude: 1)"PJRT" is a common cause of chronic incessant SVT and should be suspected in pts with relatively slow SVT with negative P waves in leads 2, 3 and aVF, 2) Differentiation of pts who will develop MD is difficult and dictates close follow-up, 3) Treatment of SVT is usually not effective with traditional medical management, 4) Encainide is frequently effective in suppressing SVT, 5) Cryoablation of the posterior septum has been curative without producing complete AV block.

SUPRAVENTRICULAR TACHYCARDIA DUE TO MULTIPLE ATRIAL ECTOPIC FOCI: A RELATIVELY COMMON PROBLEM. Arthur Garson, Jr., MD, FACC, Richard T. Smith, Jr., MD, Jeffrey Moak, MD, David A. Ott, MD, Paul C. Gillette, MD, FACC, Victoria L. Evans, MD, and Pat M. Duncan, RN. Lillie Frank Abercrombie Section of Cardiology, Texas Children's Hospital, Houston, Texas.

Atrial ectopic focus (AET) is a common mechanism for chronic "incessant" SVT in children. The majority of pts require treatment because of symptoms or tachycardia-induced cardiomyopathy. Management with traditional drugs fails to restore sinus rhythm and surgery has been thought to be curative. We have had 32 pts with AET; 18 had attempted surgical treatment; all 18 had a single abnormal P-wave axis before surgery, had mapping in the EP lab, and were thought to have a single focus. However, in 9/18 (50%) after surgical removal of this focus, additional foci became apparent. In 6/9, the next focus appeared during surgery; between 3-15 additional foci were identified and surgically treated. This resulted in cure in 4/6 but 2/6 despite almost total atrial disconnection, continued to have AET. The other 3 pts with multiple foci had AET recur with a different P-wave axis from 1 wk-2 mo postop. These have not had reop. Since the overall success rate for multiple foci (MF) (4/9) was so different from single foci (SF) (9/9), we compared MF and SF to try to predict MF. MF had: the same incidence of cardiomyopathy (78%), faster maximum atrial rate on Holter (89% of MF >160/min vs 43% of SF, P<.05), faster minimum atrial rate on Holter (89% of MF >70/min vs 0% SF, P<.05), and different preop ECG (0% MF had left atrial P-waves vs 44% of SF, P<.025). In conclusion: 1. Approximately half the pts with AET had MF. 2. Surgical treatment of MF is less successful than SF. 3. MF are unlikely with LA P-waves and slower atrial rates. We speculate that AET may have different etiologies: MF may be due to extensive atrial disease such as that found in primary cardiomyopathy or after myocarditis, whereas SF may be a developmental aberration.

ELECTRICAL ABLATION OF ATRIAL MUSCLE: EARLY AND LATE ELECTROPHYSIOLOGIC OBSERVATIONS IN CANINE ATRIA

Jeffrey P. Moak, MD, Richard A. Friedman, MD, Gregory Clark, Arthur Garson Jr., MD, FACC, Texas Children's Hospital, Houston, Texas.

Control of ectopic RA focus tachycardia or reciprocating AV tachycardia has been attempted with the electrode catheter ablative technique (ECA). This procedure has had variable effectiveness. Our purpose was to assess the electrophysiologic effects of ECA on atrial tissue, one of the determinants of ablation efficacy. Eight beagle puppies (P) underwent RA ECA using an energy dose between 100-200 joules. Twenty-four hrs after ECA, the RA from 4P was studied by standard microelectrode techniques (ME) (group I). Four P had a clinical EPS prior to and 11 wks after ECA. These 4P were then studied by ME (group II). The cellular atrial action potential characteristics in the ECA border zone of Group I was: MDP= 76 +/- 2 vs 60 +/- 4* mv; $\dot{V}$ max= 168 +/- 24 vs 68 +/- 31* V/sec; APD 90= 147 +/- 12 vs 149 +/- 28 msec in normal cells (NC) and ablated cells (AC), respectively. (*=p<.05). A central zone of "dead cells" (DC) was observed in the ECA region. Peripheral to this central zone were islands of DC surrounded by NC. No spontaneous automatic rhythms were observed and no triggered activity was elicited in group I. In group II, clinical EPS showed inducible NS Atr Fib in 4/4P. Prior to ECA, 1/4 P had inducible NS Atr Flt. ME study showed MDP= 76 +/- 1 vs 73 +/- 2* mv; $\dot{V}$ max was 164 +/- 20 vs 134 +/- 27* V/sec; APD 90= 140 +/- 8 vs 134 +/- 21 in NC and AC, respectively. Conduction block into the central ECA region occurred in all 4P; 2/4P had inducible atrial echoes in vitro. In conclusion, ECA can necrose small areas of atrial muscle. Clinical failures of ECA may be secondary to NC within the ECA region. ECA may produce a substrate responsible for late reentrant atrial arrhythmias.

ENCAINIDE: A SPECIFIC DRUG FOR PERMANENT JUNCTIONAL RECIPROCATING TACHYCARDIA (PJRT) IN CHILDREN. Janette Strasburger, MD, Richard T. Smith, Jr., MD, Jeffrey P. Moak, MD, Pat McVey, RN., Arthur Garson, Jr., MD. Lilly Frank Abercrombie Section of Cardiology, Texas Children's Hospital, Houston, Texas.

The permanent form of junctional reciprocating tachycardia (PJRT) is responsible for half of the cases of incessant, chronic supraventricular tachycardia (SVT) in childhood. It has also been called "atypical AV node reentry" or "fast-slow" SVT and is thought to be due to a slowly conducting type of bypass tract that forms the retrograde limb of SVT. PJRT is resistant to all conventional anti-arrhythmic drugs. Encainide (E) slows conduction in both the AV node and bypass tracts in adults with SVT. Because of these properties, we gave oral E to 9 children, ages 12 months to 19 years (median 4 years) with PJRT refractory to 1-4 previous medications. PJRT was present 10-100% of day with heart rates of 187-274/min. Four of 9 had secondary cardiomyopathy. Effective E doses ranged from 60 to 120 mg/m^2/day given QID. E caused prolongation of 22% in PR, 21% in RP, 34% in QRS, and 10% in corrected QT intervals. Eighty percent of SVT episodes terminated in the retrograde direction. In 1-6 months follow-up, E was effective in 7/9: E alone eliminated 99% of incessant SVT episodes in 5/9 patients (pts). E efficacy increased when combined with verapamil or propranolol in 2/9; the other 2 had inadequate response to combined therapy. No pts experienced symptoms from the drug. One pt had a ventricular tachycardia episode on 99 mg/m^2/day related to QRS aberrancy. Left ventricular shortening fractions improved in all 4 pts with cardiomyopathy from a mean of 26 to 38%. Encainide is a very effective drug in PJRT, a previously untreatable form of SVT. Cardiomyopathy resolved in children when encainide effectively controlled PJRT.

AUTOMATIC ECTOPIC ATRIAL TACHYCARDIA IN CHILDREN: IS ABLATION NEEDED?: Ashok V. Mehta, MD, FACC; L. Ewing, MD; E. Sacks, MD, FACC; A. Balian, MD; G.R. Sanchez, MD; St. Christopher's Hospital for Children & Temple Univ. School of Medicine, Phila., PA.

Automatic ectopic atrial tachycardia (AAT) is uncommon, and considered generally resistant to medical therapy; surgical or catheter ablation has been recommended. We followed 8 AAT patients (pts) with the following features: 3 males, 5 females; age at onset: intrapartum-15 yrs (median 2 yrs); no family history of SVT; no structural heart disease; LV dysfunction clinically in 3 pts and by echocardiogram in 5/7 pts; rate 220 to 280/min in 7 pts; "p" axis during SVT 0 to +90° in 6 pts and 0 to -90° in 2 pts. The diagnosis was confirmed by EP study in 6 pts. Digoxin (D) alone did not initially suppress tachycardia in 7/7 pts but improved LV function. Class 1A agents (IV procainamide 2 pts, oral quinidine 3 pts) worsened the AAT in 4/5 pts. D+propranolol suppressed AAT in 2/5 pts (both newborn) and propranolol alone in 1 pt. One pt had unsuccessful surgical ablation of the ectopic focus and another had unsuccessful transcatheter electrical ablation (25 joules). Three pts had a successful trial of IV amiodarone during EP study. Four pts, who were maintained on oral amiodarone, had good control of AAT (52 pt-months). During follow-up of 10 months to 7.5 yrs (median 2 yrs), 3 pts were free of AAT without medications, 3 pts were well controlled on medication (2 pts amiodarone, 1 pt D), 1 pt on amiodarone, who had unsuccessful surgical ablation and permanent VVI pacemaker, died suddenly, and 1 pt was lost to follow-up.

We conclude that 1) Digoxin+propranolol or amiodarone (IV and oral) is helpful in suppressing AAT, 2) Class 1A agents are contraindicated in AAT 3) AAT may resolve spontaneously during follow-up (3/7 pts) and surgical or catheter ablation may not be warranted.

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Tuesday, March 11, 1986
2:00PM–3:30PM, Room #267
Myocarditis: Biopsy

INTEROBSERVER VARIABILITY IN THE PATHOLOGIC DIAGNOSIS OF ENDOMYOCARDIAL BIOPSIES

Jeffrey G. Shanes, M.D., F.A.C.C., Jalal Ghali, M.D., Margaret E. Billingham, M.D., F.A.C.C., Victor J. Ferrans, M.D., Ph.D., John J. Fenoglio, M.D., F.A.C.C., William E. Edwards, M.D., F.A.C.C., Cheng C. Tsai, M.D., Jeffrey E. Saffitz, M.D., Ph.D., Jeffrey Isner, M.D., F.A.C.C., Jose Manaligod, M.D., Ph.D. George T. Kondos, M.D., Ramiah Subramanian, M.D., University of Illinois Hospital, Chicago, Illinois.

Controversy exists over the value of endomyocardial biopsy(EMB) in evaluating patients(pts) with dilated cardiomyopathy(DCM) particularly in regards to detecting myocarditis and the value of EMB in assessing prognosis. Interobserver variability, if high, could explain conflicting reports. To assess for this, we submitted biopsy specimens from 16 pts with DCM to 7 cardiac pathologists (ABCDEFG). The same slides were independently reviewed by each and assessed for fibrosis(F), hypertrophy(H), nuclear changes(NC), on a 0 to 3+ scale, mean lymphocyte count per HPF (LC) and myocarditis(M). The percent incidence of significant (≥ 2+) F,H,NC,LC > 5 cells/HPF and diagnosed myocarditis or borderline myocarditis (BM) was:

	A	B	C	D	E	F	G
F (%)	25	25	13	43	38	6	25
H (%)	69	44	31	19	13	88	88
NC(%)	69	38	43	31	69	75	43
LC(%)	19	13	0	13	31	0	0
M (%)	0	25	0	13	38	0	6
BM(%)	6	18	0	13	6	6	0

One or more pathologists diagnosed either myocarditis or borderline myocarditis in 11 of the 16 pts. Of these 11 pts, 4 pathologists agreed in 1 pt, 3 in 2 pts, and 2 pathologists agreed in 3 pts.

We conclude that interobserver variability is high in interpreting biopsy specimens from pts with DCM. This study supports that quantitative and standardized methods are needed to increase diagnostic consistency.

RARITY OF MYOCARDITIS ON ENDOMYOCARDIAL BIOPSY IN PATIENTS WITH NEW ONSET IDIOPATHIC CONGESTIVE HEART FAILURE. A HISTOLOGIC AND ULTRASTRUCTURAL, IMMUNOHISTOCHEMICAL AND VIRAL SEROLOGIC ANALYSIS OF 72 PATIENTS

Bruce F. Waller, M.D. F.A.C.C., John D. Slack, M.D., F.A.C.C., James C. Dillon, M.D., F.A.C.C., Michael J. Mirro, M.D. F.A.C.C., Kevin Kelly, M.D. F.A.C.C., Russel P. Valentine, M.D. F.A.C.C., Moo Noo Yum, M.D., Morris L.V. French, Ph.D. Indiana University Medical Center, Indianapolis.

Marked diagnostic variability (3 to 63%) exists in the evaluation of endomyocardial biopsies (EMB) in clinical settings in which acute myocarditis is suspected. We performed a comprehensive laboratory analysis of EMB and blood serum from 72 patients (pts) (aged 17-64 years, mean 41;54 males) with onset of congestive heart failure 2 to 24 weeks (mean 63 days) before EMB each pts was clinically suspected of having myocarditis. We assessed 360 EMB from right (43 pts, 215 EMB or left (29 pts, 145 EMB) ventricular walls with light and electron microscopy, immunohistochemical tissue markers, and viral cultures. In addition, neutralization or complement fixation titers for 22 viruses were analyzed on blood serum. Histologic results were: possible myocarditis = 1 (2%) pt, no myocarditis = 71 (98%) pts. Electron microscopy did not alter the histologic diagnoses. All samples for viral culture were negative and all serologic serum testing was nondiagnostic for recent viral infections. Thus, we found an extremely low frequency (2%) of myocarditis on EBM (2%) in a population of pts clinically suspected of myocarditis. Multiple laboratory studies beyond light microscopy did not alter the frequency of myocarditis diagnoses.

HETEROGENOUS ADRENERGIC RESPONSE OF THE MYOCARDIUM TO CONGESTIVE FAILURE.

Gordon L. Pierpont, M.D., Ph.D., F.A.C.C., Gary S. Francis, M.D., F.A.C.C., Eugene G. DeMaster, Ph.D., Maria T. Olivari, M.D., W. Steves Ring, M.D. and Jay N. Cohn, M.D., F.A.C.C., VA Medical Center and University of Minnesota, Minneapolis, Minnesota.

The adrenergic nervous system is likely important in the pathophysiology of congestive heart failure (CHF). Previous studies have suggested that normaly high concentrations of myocardial norepinephrine are depleted in CHF because of high adrenergic tone. We tested the general applicability of this theory by examining left ventricular catecholamines (multiple biopsies) and plasma norepinephrine (NE) in 28 patients (pts) with severe CHF undergoing cardiac transplantation. Plasma NE was elevated in all (ave. 828±529 μg/ml), but cardiac NE was quite variable, ranging from 79 to 2,127 ng/gm (ave. 491±402). Cardiac dopamine (DA) also varied considerably (range 0 to 713, ave. 154±164 ng/gm). Cardiac epinephrine was consistently low or undetectable. Fourteen pts had the classic pattern of low cardiac NE and elevated DA, consistent with high adrenergic tone depleting NE while DA increases because of DA conversion to NE being the rate-limiting step in NE synthesis. On the other hand, cardiac catecholamines were normal (high NE, low DA) in 5 pts; both NE and DA low in 3 pts; and NE levels preserved but DA high in 6 pts. Cardiac NE correlated only weakly with age ($r = -.45$, $p<.05$), and examination of multiple other variables failed to reveal likely causes of the differences in cardiac NE and DA. We conclude that the cardiac adrenergic response is not uniform among pts with severe CHF, and further attempts to delineate the factors regulating cardiac catecholamine concentratration and adrenergic function in such pts are needed.

EXPERIMENTAL CANINE MODEL OF HEART FAILURE PRODUCED BY RAPID VENTRICULAR PACING: CARDIAC EFFECTS

John R. Wilson, M.D., Nancy Ferraro, R.N., Rita A. Falcone, M.S., Pamela Douglas, M.D., William Hickey, M.D., Ali Muhammad, Nathaniel Reichek, M.D.
Hospital of the Univ. of Pennsylvania, Philadelphia, PA

Chronic rapid ventricular pacing reportedly produces a useful model of low output heart failure in the dog. However, little information is available regarding cardiac morphological and functional changes in this model. Accordingly, we compared hemodynamic, echocardiographic, and post mortem cardiac findings in 9 control dogs (C) and in 8 dogs paced continuously at 260 beats/min for 3 weeks (P). Echo studies in P dogs were performed with pacers temporarily reprogrammed to 20 beats/min. At 3 weeks, the paced dogs exhibited reduced cardiac outputs (C: 147±21 vs P: 112±19 ml/min/kg) and elevated pulmonary wedge (C: 8±3 vs P: 26±5 mmHg) and right atrial pressures (C: 3±2 vs P: 13±3 mmHg) (all $p<.001$). Over 3 weeks, left ventricular (LV) echo diastolic dimension increased in paced dogs (3.6±.6 to 4.3±.6 cm ($p<.01$)) but not in C dogs (3.2±0.4 to 3.4±.5 cm (p=NS)). Pacing also decreased overall %LV shortening (34±6% to 17±7%) associated with a disproportionate deterioration of posterior wall thickening (58±16% to 17±18%) ($p<.01$). At post mortem, paced dogs had larger LV volumes (C: .8±.3; P: 1.4±.3 ml/kg body weight) and RV volumes (C: .8±.2 vs P: 1.3±.4 ml/kg) (both $p<.001$). LV and right ventricular mass were similar in both groups. In 3 additional paced dogs, echo and hemodynamic data were serially measured for 3 weeks after termination of pacing. Cardiac hemodynamic and echocardiographic abnormalities returned to baseline by 1-2 weeks. These data suggest that rapid ventricular pacing in the dog produces reversible biventricular dilation and failure with severe regional dysfunction of the posterior LV wall.

ANTHRACYCLINE CARDIOTOXICITY & DILATED CARDIOMYOPATHY: MORPHOMETRIC DISTINCTIONS

Reed A. Rowan, Ph.D., Marilyn A. Masek, B.A., and Margaret Billingham, M.B., B.S., F.A.C.C., Department of Pathology, Stanford University School of Medicine, Stanford, CA.

Computer-assisted ultrastructural morphometric methods were used to measure right ventricular endomyocardial biopsies from 10 patients with idiopathic dilated cardiomyopathy (IDCM) and 10 cancer patients with anthracycline cardiotoxicity (AC), and in control biopsies from 10 healthy transplant donor hearts. Our purpose was to establish a standard for representative cases to be used for diagnostic grading and research. Results are presented in the following table as a mean ± SE (* indicates a significant difference vs controls, $p < 0.01$ or less).

	CONTROL	IDCM	AC
myocyte width, μm	16.8±0.5	29.2±.9*	19.2±0.7*
nuclear area, μm^2	45.2±1.8	88.8±5.5*	54.2±3.0*
nuclear form factor	0.44±0.01	0.28±0.01*	0.46±0.01
nucleolar area, μm^2	2.27±0.09	2.55±0.16	2.54±0.15
nucleoli per nucleus	1.03±0.02	1.6±0.09*	1.3±0.06*
mitochondrial area, μm^2 myocytes < 25 μm width	0.35±0.01	0.32±0.02	0.33±0.01
mitochondrial area, myocytes > 25 μm width	----	0.28±0.01*	0.28±0.02*
mitochondrial area, affected myocytes	----	0.28±0.01*	0.27±0.01*.

These results show that hypertrophy and bizarre nuclear form is significantly greater in IDCM than AC, suggesting not only a different mechanism of development but also a possible difference in the rate of progression of the two conditions.

DOES REPEAT ENDOMYOCARDIAL BIOPSY AID IN THE DIAGNOSIS OF ACTIVE MYOCARDITIS?

G. William Dec, M.D., John T. Fallon, M.D., Ph.D., Judith M. Scheer, RN, James Southern, M.D., Ph.D., Igor F. Palacios, M.D., F.A.C.C., Massachusetts General Hospital, Boston, MA.

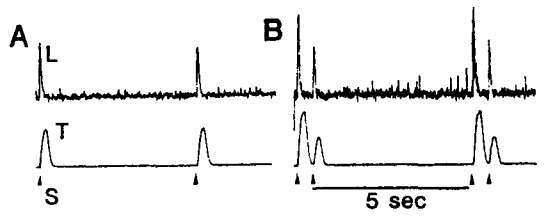
The diagnosis of myocarditis requires pathologic confirmation of myocardial necrosis (MN) and cellular infiltration (CI). Yet, myocarditis is a focal or multifocal process and sampling error during endomyocardial biopsy (bx) may occur. We studied the role of repeat bx in 13 patients (pts) in whom the clinical suspicion of myocarditis was high but whose initial right ventricular (RV) bx failed to provide histologic confirmation. All pts presented with dilated cardiomyopathy, a left ventricular ejection fraction ≤ .40, and symptomatic heart failure. Heart failure was of six months duration or less in 10 pts; 3 pts had at least one previous episode of biopsy-verified myocarditis and had repeat bx performed at the time of worsening symptoms to rule out disease reactivation. All pts underwent repeat RV bx and 10 pts concurrent left ventricular (LV) bx between 1-4 weeks of initial RV bx. Repeat bx demonstrated non-specific histologic findings including myocyte hypertrophy and interstitial fibrosis in 11 pts. Myocarditis was diagnosed in 2 pts (15%). MN and CI were detected on RV bx in 1 pt and on both RV and LV biopsies in another pt whose initial RV bx one week before had been negative. In addition, no histologic differences were seen between concurrent RV and LV biopsies. We conclude that repeat RV or LV bx can identify an additional number of pts with myocarditis which was not identified on initial RV bx.

Tuesday, March 11, 1986
4:00PM-5:30PM, Room #267
Control of Contractile Function

MECHANISM OF POST-EXTRASYSTOLIC POTENTIATION.

Judith K. Gwathmey, V.M.D., Ph.D., Roderick MacKinnon, M.D., James P. Morgan, M.D., Ph.D. Beth Israel Hospital, Boston, MA.

We tested the hypothesis that the positive inotropic effect of post-extrasystolic potentiation (PEP) is due to an increased availability of intracellular Ca^{2+} ($[Ca^{2+}]_i$) for activation of the myofilaments by use of aequorin, a bioluminescent indicator that emits light (L) when it combines with Ca^{2+}. Papillary muscles of ≤ 1 mm diameter were isolated from adult male ferrets, and perfused in an oxygenated physiologic salt solution at 30°C. Aequorin was loaded chemically; L and isometric tension (T) were simultaneously recorded. In the figure below, panel (A) shows T, L (i.e., $[Ca^{2+}]_i$) and stimulus artifact (S) when the muscle was stimulated at 5 sec intervals. Panel (B) shows T, L, and S when the muscle was given a pair of stimuli 0.5 sec apart at 5.5 sec intervals. Following the first stimulus of the pair the amplitudes of both L and T were significantly increased. These results demonstrate that PEP and the positive inotropic effect of paired stimulation are associated with an increased availability of $[Ca^{2+}]_i$ for activation of the myofilaments.



Spontaneous Contractions in Rat Cardiac Muscle

Peter P. de Tombe, B.Sc., Henk E D J ter Keurs, M.D., Ph.D., Barbara J M Mulder, M.D., Lucio Ricciardi, M.D.; The University of Calgary, Alberta, Canada

Calcium overload of cardiac cells leads to spontaneous contractions (SC) which may lead to arrhythmias. SC were studied in rat cardiac trabeculae, superfused with oxygenated Krebs-Henseleit solution at 21 C with Nomarsky microscopy combined with analysis of video recordings and laser diffraction techniques. Propagation of SC occurred at low stimulus rates within the limits of one cell as regional waves of sarcomere shortening which propagated at low speed (<50 μm/s) or as synchronized contractile waves which traveled from intercalated disc to intercalated disc at a speed of 75 to 125 μm/s. In each case SC were absent in the first 400 msec following a twitch. After a train of electrically evoked contractions at 2 Hz, spontaneous local sarcomere shortening was observed throughout a 250 μm long region close to one end of the preparation, damaged by dissection. The wave of local sarcomere shortening propagated along the whole trabecula. The velocity of propagation increased from 0 to 10 mm/s in proportion to the number of stimuli (3-30) in the train at external calcium ion concentration of 1.5 mM. At a constant number of stimuli, the velocity of propagation increased from 0-15 mm/s with increasing extracellular calcium ion concentration. Propagation of SC at low and variable velocity is consistent with the hypothesis that calcium leakage into damaged cells induces calcium release from the sarcoplasmic reticulum. This process propagates as a result of diffusion of calcium into adjacent cells which may trigger calcium release from their sarcoplasmic reticulum. The observed propagation velocities could be predicted with the aid of a mathematical model of calcium induced calcium release.

NORMAL INOTROPIC RESPONSE OF THE HYPERTROPHIED LEFT VENTRICLE TO SPECIFIC β_1 ADRENERGIC STIMULATION IN CONSCIOUS DOGS.
Alan M Fujii, MD, Israel Mirsky, PhD, Juan Serur, MD, Ann Als, MD, Stephen F Vatner, MD. Harvard Med Sch, N E Reg Primate Res Ctr, Southboro, MA

Reduced inotropic responsiveness to β adrenergic receptor agonists norepinephrine and isoproterenol, agents which substantially affect afterload, is commonly reported in anesthetized animals with LV hypertrophy (H). We studied inotropic responses to prenalterol (PRE), a specific β_1 adrenergic receptor agonist which has little effect on afterload, in conscious dogs with severe LVH induced by aortic (A) banding in puppies. One to 2 yrs later the dogs with LVH [LV/body weight ratio 7.0±0.4 vs 4.0±0.2 g/kg ($p<0.01$) in control dogs] were instrumented with ultrasonic crystals to measure LV diameter (D) and wall thickness, miniature LV pressure (P) transducers and A catheters. Baseline LV systolic/end-diastolic P was 115±2/8±1 mmHg in controls and 221±12/11±1 in dogs with LVH. In 6 control dogs PRE (8 mcg/kg/min) increased LV dP/dt from 3174±299 to 5210±523 mmHg/sec, dD/dt/D from 1.77±0.06 to 2.78±0.22/sec and mean velocity of circumferential fiber shortening (VCF) from 1.25±0.08 to 1.72±0.11/sec, while mean AP and mean systolic wall stress did not change from 96±3 mmHg and 193±17 dynes/cm^2, respectively. In 6 dogs with LVH PRE increased LV dP/dt from 3129±70 to 5611±348 mmHg/sec, dD/dt/D from 1.69±0.21 to 2.60±0.31/sec and VCF from 1.18±0.14 to 1.82±0.20/sec, while mean AP and mean systolic wall stress did not change from 93±5 mmHg and 220±14 dynes/cm^2, respectively. Thus, in conscious dogs with severe stable chronic LVH, baseline LV function is normal as is the inotropic response to β adrenergic receptor stimulation in the absence of a significant change in afterload.

CONTRACTILE PROTEIN CONTENT IS INCREASED IN HYPERTROPHY STIMULATED BY NOREPINEPHRINE BUT NOT BY A PHORBOL ESTER: AN EXAMPLE OF PATHOLOGICAL HYPERTROPHY IN CULTURED NEONATAL RAT HEART MUSCLE CELLS
Neal White, M.D., Tanny Tsao, M.S. and Paul Simpson, M.D.,F.A.C.C. VAMC, CVRI and Univ. Calif., San Francisco

We have previously found that norepinephrine (NE) stimulates hypertrophy of nondividing neonatal rat heart muscle cells in serum free cultures and that this response is mediated by an alpha-1 adrenergic receptor. A tumor promoter, phorbol 12-myristate 13-acetate (TPA) also stimulates hypertrophy. We asked whether contractile protein content was increased in these two types of hypertrophy. Cell cultures were treated for 48-72 hours with NE (2μM), TPA (20-200nM) or TPA + NE (20-200nM and 2-20μM respectively). Total Protein (TP), was quantified by the method of Bradford and by a radioisotopic assay; and myosin heavy chain (MHC), by densitometry after SDS-PAGE. NE increased TP and MHC per cell. TPA increased TP but did not change MHC. TPA + NE was similar to TPA alone.

	TP *	MHC *	MHC/TP *
	100	100	100
CONTROL(n=6)			
NE (n=5)	158.7±11.8 ΔΔ	209.7±19.7 ΔΔ	133.6±13.6 Δ
TPA (n=6)	132.9±5.2 ΔΔ	107.5±8.3	80.9±5.3 ΔΔ
TPA+NE(n=5)	150.3±6.8 ΔΔ	117.0±10.6	78.2±6.9 ΔΔ

* Values are % of control expressed as mean ± SE
ΔΔ $p<0.01$ vs. control and Δ $p<0.05$ vs. control

Conclusion: Our results demonstrate that cells enlarged by NE have increased contractile protein, whereas cells enlarged by TPA do not. We suggest that selective failure of contractile protein accumulation is one possible mechanism for the genesis of a pathologically hypertrophied cell.

BOTH PHENYLEPHRINE AND METHOXAMINE AFFECT LEFT VENTRICULAR CONTRACTILE PERFORMANCE
Marvin W. Kronenberg, M.D., F.A.C.C., David W. Grambow, Robert W. McCain, Robert J. Boucek, M.D., Gordon A. Moreau, M.D., Kiichi Sagawa, M.D., Gottlieb C. Friesinger, M.D., F.A.C.C., Vanderbilt U., Nashville, TN.

Pharmacologic vasoconstriction is used to study left ventricular (LV) systolic pressure-volume relations in man, but the effects of these agents on the myocardium itself are understood incompletely. The effects on contractility of phenylephrine (PE) and methoxamine (MTX) were studied using dose-response relations. Isovolumic LV pressure (LVP) was employed to estimate contractility in isolated blood-perfused rabbit hearts (N=14) (Expt. 1). Mean arterial pressure (MAP) changes were studied in intact rabbits (N=10) (Expt. 2).

%Change vs. Control	10^{-5}M PE	10^{-4}M MTX
LVP(Expt 1)	+24±24	-35±15
MAP(Expt 2)	+82±32	+56±15 (mean ± SD).

Each of these effects was significant ($p< .01$). Propranolol reduced PE's effect on LVP (N=5, $p<.01$). To simultaneously compare LVP and MAP, 5 isolated hearts were cross-circulated with blood from instrumented support-animals during PE or MTX infusion (expt. 3). Both isolated-heart LVP and support-animal MAP were increased by PE. Paradoxically, LVP decreased 19±6% while MAP increased 27±13% after MTX.

Summary: PE increases LV contractility, primarily by beta-adrenergic effects. Conversely, there are direct myocardial depressant effects of MTX at doses which produce peripheral vasoconstriction. These results emphasize the limits of pharmacologic manipulation of arterial blood pressure in assessing myocardial contractility.

EFFECTS OF SEX HORMONES ON CARDIAC FUNCTION IN FEMALE RATS.
Thomas F. Schaible, Ph.D., Alwyn Murphy, Gary Ciambrone and James Scheuer. Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY

Testosterone profoundly supports cardiac function in the male rat. To examine the cardiac effects of sex hormones in adult female rats, hearts were studied from rats gonadectomized (GX) at 10 wks of age and compared at 20 wks to age-matched sham-operated rats. Sex hormones were replaced for 10 wks in GX: either 2ug estradiol (E)/day (GXE); 0.4mg progesterone (P)/day (GXP); combined E and P (GXEP); or 2mg testosterone (T)/day (GXT). Isolated working hearts were studied at constant left atrial pressure, aortic pressure and heart rate. Results were: (n=8-10, +$p<0.05$ vs GX, °$p<0.05$ vs SH)

	Sham	GX	GXE	GXP	GXEP	GXT
BW	280+	321°	275+	337°	281+	347°+
DHW	155	159	154	163	148	190°+
SW	2.26+	1.96°	2.47+	1.78°	2.43+	2.90°+
FS	14.9+	13.6°	15.3+	13.1°	15.4+	17.9°+
VCF	2.35+	2.11°	2.37+	2.07°	2.32+	2.53+

(BW=body weight (g); DHW=dry heart weight (mg); SW=stroke work (ergs. 10^5 per DHW); FS=fractional shortening at midwall (%); VCF=mean velocity of circumferential fiber shortening (circ/sec)).

GX increased body weight and decreased cardiac function which was corrected by treatment with E, but not P. Treatment of GX with T increased body and heart weight and cardiac function when compared with GX or SH. Therefore, E but not P may regulate cardiac function in female rats, whereas T has profound effects on both cardiac mass and function in female rats.

Tuesday, March 11, 1986
2:00PM–3:30PM, Room #268
Cell Studies and Automatic Rhythms

PLATEAU CURRENTS IN CANINE VENTRICULAR MYOCYTES

G-N. Tseng, Ph.D., R.B. Robinson, Ph.D., and B.F. Hoffman, M.D.,F.A.C.C. Department of Pharmacology, Columbia University, New York, NY 10032

Drugs may exert therapeutic or toxic effects by affecting the plateau phase (P) of the cardiac action potential (AP). Plateau currents were studied in rod-shaped myocytes isolated from left ventricles of adult dogs. The cells had a resting potential of -84 mV in 4 mM K and AP characteristics similar to those of intact tissues. Voltage clamp was done with the single microelectrode method. Transient outward current (I_{to}) was activated positive to -20 mV and showed voltage-dependent inactivation between -80 and -50 mV. I_{to} had a time to peak (TTP) of 10 msec and decayed with a time constant (τ) of 10-20 msec. Slow inward current (I_s) was activated positive to -30 mV and showed voltage-dependent inactivation between -50 and -20 mV. I_s had TTP of 5-10 msec and decayed with a τ of 40-100 msec. Delayed rectifier current (I_x) was activated positive to -20 mV and increased with a τ of 100-200 msec. The P configuration and duration showed a complicated dependence on the holding voltage (V_h) preceding the AP: as V_h changed from -80 to -60 mV, AP shortened along with a decrease in upstroke velocity; from -60 to -40 mV, AP prolonged along with a decrease in notch depth and a positive shift in P voltage; from -40 to -20 mV, AP markedly shortened along with a negative shift in P voltage. These changes could be explained by the voltage-dependence of "window" Na current, I_{to}, I_s, and I_x. We conclude that all these four currents contribute to the plateau phase of canine ventricular action potentials.

EFFECT OF PROCAINAMIDE ON ANISOTROPIC CONDUCTION-MECHANISMS

Alan Kadish, MD, Joseph F. Spear,PhD, FACC Joseph H. Levine, MD, E. Neil Moore DVM, PhD, FACC University of Pennsylvania, Philadelphia, Pa.

We found that procainamide (PCA) decreases conduction velocity in anisotropic canine ventricular muscle by a mean of 10% longitudinal (LG) to fiber orientation and only 5% transverse (TV) to it. Using action potential parameters and a cable theory model we calculated the LG and TV specific internal resistance in six preparations. The ratio of LG to TV conduction velocity decreased from 3.25 to 3.05 after 20 ugm/ml PCA ($p<0.05$). Internal resistance LG to fiber orientation was relatively unchanged (250 vs 267 Ω-cm) but TV to it decreased by 9% (3324 to 3039 Ω-cm). To examine whether differences in drug binding depending on propagation direction also may contribute to the preferential depression of LG conduction, we examined conduction during sudden changes in pacing direction in 5 preparations perfused with PCA. At a cycle length of 1000 msec, conduction velocity (normalized to control) was 5% lower LG than TV to fiber orientation and there was no difference between steady state conduction velocity in a given direction and that in the first few beats after a direction change. At cycle lengths of 600 and 400 msec normalized conduction velocity LG to fiber orientation was lower in the first few beats after a change in propagation direction from TV to LG and decreased further with continued pacing. We conclude: 1) At a pacing cycle length of 1000 msec, the less marked depression of TV conduction by PCA is due to a decrease in internal resistance TV to fiber orientation 2) At shorter pacing cycle lengths, greater drug binding during LG pacing contributes to the differential effect of PCA. 3) The varying activity and binding of PCA depending on cycle length and fiber orientation may help explain the heterogenous response to its clinical use.

DEVELOPMENTAL AND USE-DEPENDENT EFFECTS OF PHENYTOIN ON NEONATAL AND ADULT PURKINJE FIBERS.

Walter Spinelli, Ph.D. Michael Rosen, M.D.,F.A.C.C., Columbia University, N.Y.

Age-related changes in the actions of antiarrhythmic drugs have been observed clinically and experimentally. One drug, phenytoin (P) has been reported particularly effective in the treatment of postoperative ventricular arrhythmias in children. In this study we: a) tested whether developmental differences in P action on the transmembrane action potential (AP) of Tyrode's superfused canine Purkinje fibers might explain the clinical observations; and b) evaluated the contribution of use-dependent reduction of $\dot{V}_{max}$ and effects on slow responses to P's antiarrhythmic action. We studied the effects of P in a concentration range of 1.5-50 ug/ml. P concentrations of 5 and 10 ug/ml (comparable to therapeutic plasma levels) had no major effects on AP characteristics or frequency-dependent effects at either age at $[K^+]_o$=4 mM. At [K]=6 mM, on decreasing the drive cycle length from 1300 to 300 msec, P reduced $\dot{V}_{max}$ by 25 and 40% at 5 and 10 ug/ml at both ages. Conduction times were significantly prolonged in a dose and use-dependent manner. The time constant for onset (τ_o) and recovery (τ_r) from use-dependent block was similar in adults (A) and neonates (N) ($p>0.05$). At [P]=5 ug/ml τ_o = 1050±35 (A) and 960±120 msec (N) ($\bar{X}$±S.E.); τ_r = 319±25 (A) and 263±58 msec (N). The effects of [P]=10 μg/ml on slow responses in $[K]_o$=22 mM + isoproterenol 10^{-6}M were significant ($p<0.05$), although modest, at both ages. AP amplitude decreased 6% and $\dot{V}_{max}$ decreased ~ 19% in A and N; there was no significant slowing of conduction. This study indicates that in K^+-depolarized PF, use-dependent reduction of the fast Na current is a major determinant of the antiarrhythmic action of P. In contrast to lidocaine and quinidine, no age-related changes in P action were found, underscoring the different developmental effects of individual antiarrhythmic drugs.

DEVELOPMENTAL CHANGES IN DELAYED AFTERDEPOLARIZATIONS AND TRIGGERED ACTIVITY IN CANINE CORONARY SINUS.

Nancy Johnson, M.D., Michael R. Rosen, M.D., F.A.C.C., Columbia Univ., New York, NY.

Delayed afterdepolarizations (DAD) and triggered activity (TA) have been shown to occur in isolated adult canine coronary sinus (CCS) exposed to catecholamine, and may be a cause of atrial arrhythmias in vivo. Because there are developmental changes in cardiac arrhythmias, we studied the transmembrane potentials and the age-related development of DAD and TA in CCS, in the neonatal and adult canine heart. We used standard microelectrode techniques to study the action potentials (AP) in the control state at BCL=1000 ms of 12 adult and 12 neonatal (≤ 14 days) CCS. The mean values (±SE) were, respectively: MDP -81±1.3, -80 ±1.1 mV; Amplitude 112±3, 105±1.8 mV; $\dot{V}_{max}$ 262±38, 144±26 V/sec; AP duration to 50% repolarization (APD_{50}) 79±5.6, 54±2.8 msec; AP duration to 90% repolarization (APD_{90}) 199 ±6.6, 97±5.1 msec. Neonatal values for $\dot{V}_{max}$, APD_{50} and APD_{90} were significantly less than the adult ($p < .02$). Similar measurements were made in 6 adult and 7 neonatal CCS following 10 min exposures to increasing concentrations of epinephrine (10^{-7}-10^{-5}M). The neonatal concentration response curve for AP amplitude was shifted significantly to the right of that for the adult. All adult CCS developed DAD (max amplitude 8.9±0.4 mV) and 5 of 6 developed TA. In contrast, no neonatal CCS developed DAD or TA. Two neonatal CCS were exposed to ouabain, $2x10^{-7}$M. Both developed prominant DAD and TA within 10 min. Thus, neonatal CCS are capable of generating DAD and TA, but fail to do so in response to concentrations of epinephrine having marked effects on the adult. These differences between neonates and adults may contribute to the different spectra of arrhythmias seen developmentally.

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IN VIVO RECORDING OF EARLY AFTERDEPOLARIZATIONS PRECEDING TORSADES de POINTES

William Craelius, Ph.D., Victor Chen, Ph.D., Robert Zeiler, Ph.D., Nabil El-Sherif, M.D., F.A.C.C., SUNY, Downstate and VA Medical Centers, Brooklyn, N.Y.

An arrhythmia resembling Torsades de Pointes (TdP) spontaneously occurred during bradycardia in dogs given the inotropic agent anthropleurin-A (APA). Onset of TdP was preceded by marked QT prolongation. The arrhythmia was investigated using floating microelectrodes to record transmembrane potentials from the epicardium of seven intact dogs. Action potentials having magnitudes of 70 to 100 mV were analyzed and data from approximately 100 impalements and 55 episodes of arrhythmias are represented. During normal sinus rhythm (CL350 to 400 ms) APA (4μg/Kg) prolonged the action potential duration (APD 90) from a control value of 150 ± 40 msec to 220 ± 50 msec and caused a corresponding increase in QT interval. Slowing of heart rate with vagal stimulation to cycle lengths of 1000 msec caused marked prolongation of QT with APD's ranging from 400 ms to values greater than the diastolic interval. Brief depolarizations of 2 to 8 mV that occurred during phase 3 of prolonged action potentials were common occurrences during bradycardia. These potentials resembled early after depolarizations (EAD's) and were frequently seen prior to initiation of arrhythmias. Ventricular premature beats showing the R-on-T phenomena were initiated in association with EAD's during phase 3 of action potentials and preceded multiform ventricular tachycardia that either terminated spontaneously or degenerated into fibrillation. QT alternans associated with alternation of EAD and/or action potential duration were also commonly seen. The in vivo recording of EAD's in association with TdP provides direct evidence for an automatic initiation of the arrhythmia.

Tuesday, March 11, 1986
4:00PM–5:30PM, Room #268
Channel and Therapy-Site Specific Control of the Myocardium

CHARACTERIZATION OF A PARTIALLY PURIFIED NATURALLY OCCURRING CARDIAC CALCIUM CHANNEL AGONIST.

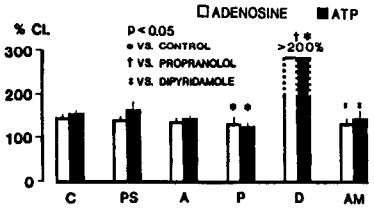
Mitchell S. Finkel, M.D., John F. Tallman, Ph.D., and Barry L. Zaret, M.D. F.A.C.C., Yale Univ. School of Medicine, New Haven, CT

Certain snake venoms may activate the cardiac voltage-sensitive calcium channel (VSCC). We, therefore, partially purified Crotalus atrox venom and characterized its effect on calcium antagonist binding to rat heart membranes using [^{3}H] nitrendipine (Nit). Nit binding was saturable from .04 to 2nM with K_1 for nifedipine = nitrendipine (<1nM); partial displacement of 40% by verapamil and 30% potentiation of binding by diltiazem at 37°. SDS gel electrophoresis of venom following purification with ion exchange chromatography revealed proteins of 15,000–60,000 molecular weight. Venom inhibited Nit binding with an IC_{50} = 6mg/ml protein. Scatchard plots revealed inhibition to be competitive with a decrease in affinity (K_D 0.6 vs 1.2nM) and no change in number (Bmax 216 vs 200 fmol/mg prot.) of binding sites in the absence and presence of venom respectively. Thus, an extract from Crotalus atrox venom competitively inhibits binding to the cardiac high affinity [^{3}H] nitrendipine binding site in doses similar to those reported to activate the voltage-sensitive calcium channel in the heart. These data support a role for this site as an agonist binding site in the heart. In addition Crotalus atrox venom provides an exciting new tool for purification of cardiac calcium channels.

ADENOSINE AND ATP SUPPRESS VENTRICULAR ESCAPE RHYTHMS IN THE CANINE HEART

Amir Pelleg, Ph.D., Hideo Mitamura, M.D., Takao Mitsuoka, M.D., Eric L. Michelson, M.D., F.A.C.C., Leonard S. Dreifus, M.D., F.A.C.C. The Lankenau Medical Research Center, Philadelphia, PA

In vitro studies suggest a negative chronotropic action of adenosine on ventricular automaticity. To study the actions of adenosine and ATP on ventricular escape rhythms in vivo, the His bundle region was electroablated in 16 closed chest dogs. All dogs exhibited stable ventricular escape rhythms with mean cycle length (CL) = 1210 ± 80 msec and QRS = 91 ± 5 msec. Adenosine or ATP (3 μmol/kg) was given into the right atrium before (control = C) and after serial iv administration of: physostigmine (PS; 50 μg/kg), atropine (A; 0.2 mg/kg), propranolol (P; 1 mg/kg), dipyridamole (D; 250 μg/kg), and aminophylline (AM; 5 mg/kg). As shown in the figure, both adenosine and ATP markedly increased ventricular escape rhythm CL, to 147 ± 7% and 157 ± 6% of baseline, respectively (each, $p < 0.01$) under control conditions. These actions were only negligibly affected by vagal enhancement (PS), vagal attenuation (A), and beta adrenergic blockade (P). However, D which selectively blocks adenosine transport and thereby its degradation, markedly enhanced the effects of both ATP and adenosine; while AM, a competitive antagonist of adenosine, reversed the effects of dipyridamole. Thus, (1) adenosine and ATP suppress ventricular escape rhythms in vivo, apparently independent of the autonomic nervous system,and (2) this action of ATP is mediated predominantly by its degradation to adenosine.



ANTIARRHYTHMIC DRUG BINDING TO VOLTAGE-SENSITIVE TOXIN RECEPTOR ON CARDIAC NA CHANNEL.

Robert S. Sheldon, M.D., Ph.D. and Henry J. Duff, M.D. University of Calgary, Calgary, Alberta, Canada

Previous studies show that local anaesthetics bind to a specific site on the nerve Na channel at physiologically active concentrations, thereby decreasing sodium influx and action potential propagation. This suggests that Type I antiarrhythmic agents might be effective by binding to a similar site on the cardiac Na channel. We tested this concept by measuring the binding of the Na channel radioligand [^{3}H] Batrachotoxinin Benzoate (BTXB) to cardiac myocytes. BTXB binding in this assay is dependent on a second Na channel toxin from Anemone sulcata (ATX). Quiescent, Ca^{++}-tolerant myocytes (80% viable) were isolated by collagenase digestion of adult rat hearts, and BTXB binding was measured by filter-binding. Myocytes were incubated at 37° with BTXB with or without ATX. ATX-dependent BTXB binding was complete within 45 min. In 1μM ATX the binding was saturable (K_D 20nM). ATX-dependent BTXB binding was voltage-dependent, as demonstrated by inhibition of binding by $BaCl_2$ or elevated KCl in the reaction. The voltage-dependent BTXB binding had a B_{max} of 10 sites/μM² cell surface, which is similar to electrophysiological estimates of Na channel density. Type I AA drugs compete with BTXB binding at pharmacologically relevant concentrations, with the same rank order of potency clinically and in vitro (r = 0.84). The stereoisomers of tocainide have a 3-fold different affinity for this site. This indicates that BTXB and Type I AA drugs bind to specific sites which have characteristics of saturability, stereospecificity, similar rank order of potency in vivo and in vitro and voltage-dependence.

EFFECTS OF VERTEBRATE DIGITALIS-LIKE SUBSTANCES ON THE CELLULAR ELECTROPHYSIOLOGIC PROPERTIES OF PURKINJE FIBERS.

R. Kieval, B.A., V.P. Butler, M.D., F. Derguini, Ph.D., R. Bruening, Ph.D., K. Nakanishi, Ph.D., M.R. Rosen, M.D., F.A.C.C., Columbia University, New York.

Substances with digitalis-like immunoreactivity are produced by several vertebrate species. There also is evidence for the existence of a digitalis-like substance of human origin. The cellular electrophysiological effects of these substances on cardiac tissues have not been reported. Therefore, we studied the effects of bufalin, an unconjugated cardiotonic steroid produced by the toad, Bufo marinus, on the action potential characteristics of 6 adult canine Purkinje fibers (PF). Bufalin ($2x10^{-8}$M) significantly reduced maximum diastolic potential (MDP) from -97± 1 to -88±2 mV ($\bar{X}$±SE) within 40 minutes of exposure. It also reduced the action potential amplitude (Amp) from 132±2 to 121±2 mV; action potential duration (APD) from 316±12 to 262±8 msec; and $\dot{V}_{max}$ from 616±35 to 493±17 V/sec (all $p < .05$). All 6 PF developed delayed afterdepolarizations (DAD), and 2 developed triggered rhythms. Ouabain demonstrated lesser potency, in that $2x10^{-7}$M ouabain was required to comparably reduce MDP, Amp, APD, and $\dot{V}_{max}$ within 30 minutes in 6 PF. All 6 showed DAD, and 2 PF developed triggered rhythms. In addition, one sample of an extract of human bile that cross-reacted with anti-digitalis and anti-bufalin antibodies, also reduced MDP, Amp, APD, and $\dot{V}_{max}$, and produced DAD and triggered activity. In contrast samples of bile without such cross reactivity had no comparable effect on the action potential. These results are consistent with other evidence that lower vertebrates and possibly humans produce digitalis-like substances. The production, and therefore possible overproduction, of a digitalis-like substance in man and other mammals may account for the occurrence of some cardiac arrhythmias which at present are considered idiopathic.

HEMODYNAMIC AND CALCIUM ANTAGONIST BINDING CHARACTERISTICS IN HAMSTER CARDIOMYOPATHY

Mitchell S. Finkel, M.D., Randolph E. Patterson, M.D. F.A.C.C., Edith H. Speir, B.S., Eric S. Marks, M.D., Kenneth Steadman, B.S., and Harry R. Keiser, M.D., NHLBI, NIH, Bethesda, MD.

We compared hemodynamics and (^{3}H) Nitrendipine (N) binding to cardiac membranes in BIO14.6 Cardiomyopathic Syrian Hamsters (MYO) at 4 and 10 mos. with their F_1B. controls. In ligand competition studies nifedipine = nitrendipine (K_i =1nM) with 60% maximal displacement by verapamil and 30% potentiation of binding by diltiazem at 37° in both myopathic and control hearts. A 50% increase in the number (Bmax) of N binding sites was seen only in the 4 mo. old MYO vs controls, with no change in affinity (K_D). (Bmax = 468 + 11 vs 309 + 10 (fmol/mg prot.); (K_D = .65 + .12 vs .75 + .14nM), MYO vs control while no differences in Bmax or K_D were seen at 10 mos. (Bmax = 375 + 9 vs 362 + 7 (fmol/mg prot.); (K_D = .82 + .18 vs .89 + .17nM), MYO vs control. Hemodynamic studies revealed no significant differences in CO, CI, SV, HR, mean arterial pressure, peripheral resistance (PR), body wt., heart wt. at 4 mos., but a significant decrease in PR (1120 + 360 vs 2080 + 240) increase in body wt. (118 + 2 vs 94 + 2 gms) and heart wt. (97 + 5 vs 78 + 2 gms/100 gm body wt.) in 10 mos. MYO vs control animals. We conclude that the onset of cardiomyopathy at 4 mos. is associated with a selective increase in N binding sites; and heart failure at 10 mos. is associated with a relative decrease in these sites. Thus, at 4 mos. the increased number of N binding sites may be compensatory, but this loss of compensation at 10 mos. results in CHF. These data support an agonist role for the high affinity N binding site in heart.

THE EFFECT OF OPIOID PEPTIDES ON THALLIUM TRANSPORT BY CULTURED MYOCARDIAL CELLS

Bruce J. Friedman, MD, FACC, Joan P. Friedman, AB, Bob Beihn, MS, Shaker Mousa, PhD, and Glen Van Loon, MD. University of Kentucky, Lexington, KY

Opioid peptides and opiate receptors are present in the heart, and have been shown to affect contractility. However, neither the action nor the mechanism of action of these peptides on the heart are fully understood. Therefore, to determine the effect of opioid peptides on monovalent cation transport, we studied their effect on thallium-201(T1) uptake by cultured chick myocardial cells, a preparation devoid of neural elements. Monolayers of synchronously contracting ventricular cells grown on coverslips were placed in a chamber and perfused to the asymptote with T1-labeled media. Radionuclide kinetics were then monitored during washout with unlabeled media. Leu-enkephalin (10^{-6}M), met-enkephalin (10^{-7}M), β-endorphin (10^{-8}M), dynorphin A 1-6 (10^{-7}M) were screened for an effect on T1 uptake. Each experiment was paired using, for control, the same coverslips and labeled followed by unlabeled perfusion media without peptide. For each peptide, dual experiments were performed alternating the sequence of peptide infusion and control. Cellular T1 uptake was determined by computer using standard formulae. Leu-enkephalin, met-enkephalin, and β-endorphin had no significant effect on T1 uptake. Dynorphin A 1-6 (10^{-7}M) significantly ($p<.05$) decreased T1 uptake. Varying concentrations from 10^{-8} to 10^{-5}M of dynorphin A 1-6 decreased T1 uptake in a dose-dependent manner. The maximal decrease in T1 uptake was 35%. We conclude that dynorphin A 1-6 has direct effects on cultured chick ventricular cells, decreasing T1 uptake in a dose-dependent fashion. This effect on monovalent cation transport may play a role in the cardiovascular effects of opioid peptides.

INHIBITION OF SODIUM WITHDRAWAL CONTRACTURES BY AMILORIDE.

Kathleen Brown, D.V.M., Augustus Grant, M.D.,Ph.D., and Harold Strauss, M.D. Duke University Medical Center, Durham, N.C.

Amiloride blocks both external Na^+-stimulated Ca^{2+} efflux and Ca^{2+} influx into Na^+ loaded cells, presumably by its blocking action on the Na-Ca exchanger. To determine if this mechanism underlies the delay in repolarization produced by prolonged exposure of canine cardiac Purkinje fibers to amiloride, we measured intracellular Na^+ activity ($\alpha_{Na}{}^i$), contractures (Ctr,mg/mm²) and membrane potential as $[Na]_o$ was reduced stepwise from 150 to 1.5mM. Removal of K^+ alone increased $\alpha_{Na}{}^i$ to 13.2±0.6mM; therefore, 1μM strophanthidin was also added to increase Na^+ loading in control fibers and fibers superfused with .01 to 1mM amiloride for 2 hr. As $[Na]_o$ was reduced from 150 -> 30mM, $\alpha_{Na}{}^i$ was linearly related (slope) to $\alpha_{Na}{}^o$. Results are summarized in table as mean ± SD.

	control	.01 A	.1 A	1 A
peak $\alpha_{Na}{}^i$	19.8±2	21.7±2	17.0±0.7	13.5±1
slope	.161±.01	.163±.01	.11±0	.068±.01
Ctr 150->30	50.7±17	43.7±11	20.6±6	29.5±10
max Ctr	53.4±24	56.8±12	43.5±11	50.5±9

Although delayed repolarization is clearly manifested, there is no evidence that .01mM amiloride inhibits Na-Ca exchange. However, Ca^{2+} entry into Na^+-loaded cells is likely inhibited by .1 and 1mM amiloride (notably at 30mM Ctr). Inhibition of strophanthidin-induced Na^+ loading by 1mM amiloride appeared to increase the contracture, possibly by interfering with Ca^{2+} efflux at a lower $\alpha_{Na}{}^i$.

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Tuesday, March 11, 1986
Poster Displayed: 2:00PM–5:00PM
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Hall D, Georgia World Congress Center
Electrophysiology—Clinical

CAROTID BAROREFLEX ABNORMALITIES AND END-ORGAN RESPONSIVENESS IN PATIENTS WITH DIABETES MELLITUS

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We studied 10 normotensive patients (pts) with insulin dependent diabetes mellitus (DM) to determine characteristics of the carotid baroreflex (CBR) and to test whether CBR dysfunction was due in part to end-organ responsiveness. Eight age-matched control pts (C) also had CBR testing. CBR was tested using neck suction pulses (-60 mmHg, .6 sec) introduced at 20-40 msec intervals throughout the cardiac cycle. Sinus node responsiveness was determined using 10 mg of iv edrophonium. Intrinsic heart rate (HR) was obtained with iv atropine (0.03 mg/kg) and propranolol (0.15mg/kg). DM pts were 45±5 ($\bar{X}$ ± SEM) years old and duration of DM was 17 ± 3 years. For DM pts CBR dysfunction varied: 3 had no increase (↑) in sinus intervals (PP) with neck suction; in 7 pts, latency for onset of PP ↑ was 526 ± 42 ms (C= 315 ± 40, p=0.003), time to maximum PP ↑ was 1014 ± 54 ms (C= 856 ± 63, p= 0.08), and maximum PP ↑ was 184 ± 46 ms (C= 197 ± 26, p= 0.8). Maximum PP ↑ for all DM pts correlated (r= .74, p= .007) with duration of DM but not with age. Edrophonium slowed HR in all 10 DM pts by 12 ± 5 b/m, and HR slowing did not correlate with maximum PP ↑ during neck suction. Intrinsic HR was within predicted range for all pts (87 ± 6 b/m). We conclude: 1) carotid baroreflex in diabetes mellitus pts compared with controls shows several abnormalities including no response and prolonged latency; and 2) carotid baroreflex dysfunction is not related to end-organ unresponsiveness.

SIGNIFICANCE OF PHARMACOLOGIC TOTAL AUTONOMIC BLOCKADE IN PATIENTS WITH SICK SINUS SYNDROME: ASSESSMENT BY DIRECT SINUS NODE RECORDINGS.

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This study was designed to assess effects of pharmacologic total autonomic blockade (TAB) (atropine 0.04 mg/kg and propranolol 0.2 mg/kg, i.v.) on sinus node automaticity in patients with sick sinus syndrome (SSS) by direct sinus node recordings. The intrinsic heart rate was determined in 22 SSS patients by TAB. In this way they were classified into 12 patients with intrinsic sinus node dysfunction (group I) and 10 patients with disturbed autonomic regulation of sinus node function (group II). Direct sinoatrial conduction time for sinus beat (SACTsb) was lengthened in group I (178±42ms→198±76ms, mean±SD, $p<0.05$) but was shortened in group II (170±63ms→126±35ms, $p<0.05$) by TAB, which resulted in significant difference in the SACTsb's of the two groups ($p<0.05$). Direct sinus node recovery time (SNRT) [=indirect SNRT-direct sinoatrial conduction time for the first postpacing beat (SACTppb)] was lengthened in group I (1622±475ms→1906±656ms, $p<0.01$) but was shortened in group II (923±81ms→785±150ms, $p<0.05$) by TAB. There was significant difference in direct SNRT either before or after TAB between group I and group II ($p<0.01$ in either). Regarding sinus node automaticity after atrial overdrive pacing for SNRT measurement, 10 patients of group II demonstrated both acceleration (corrected SNRT<SACTppb) and depression (corrected SNRT>SACTppb): 7 acceleration; 3 depression before TAB, but all 10 acceleration after TAB. In contrast, all 12 patients of group I demonstrated depression before and after TAB. This study shows that TAB combined with direct sinus node recordings may contribute to elucidation of the electrophysiologic mechanism of SSS.

HEAD-UP TILT TESTING: AN IMPORTANT TOOL IN THE WORK-UP OF RECURRENT SYNCOPE OF UNKNOWN ETIOLOGY

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Sixty-four pts with recurrent syncopal attacks (SA) which were unexplained despite extensive non-invasive investigations (including at least 48 hours of Holter monitoring) underwent blood pressure (BP) and heart rate (HR) monitoring during standardized 60° head-up tilting (HUT). Syncopal attacks were precipitated in 27 pts (42%) within 13 ± 7 min of initiation of tilting. Mechanisms underlying the event were vasovagal in 16 (drop of BP and HR), vasodepressor in 5 (drop of BP without drop in HR) and unsuspected autonomic dysfunction in 6. Abnormal responses to HUT (without syncope) were observed in another 15 pts. Three of the latter had a blunted HT response and were classified as having chronotropic insufficiency. The other 12 pts had an exaggerated increase in HR at 60± HUT. This tachycardic response was later determined to be due to idiopathic hypovolemia in 4 (125 I-HSA plasma volume measurement), marked peripheral venous pooling in 4 (orthostatic drop in cardiopulmonary volume), and hyperbeta adrenergic state in 4 (abnormal response to graded isoproterenol infusion). Twenty-two patients (34%) had a normal response to HUT.

Conclusion: 1) HUT is a safe and valuable provocative tool in the work-up of unexplained recurrent SA. 2) Abnormalities of autonomic tone are frequently present in pts with recurrent SA. 3) Coupled with appropriate non-invasive tests, HUT allowed specific diagnosis of the syncopal mechanisms in 42% of pts tested and helped delineate hemodynamic and/or volume abnormalities that may well be contributory to SA in another 23% of pts.

DIVERGENT EFFECTS OF HYPOTHERMIA, QUINIDINE AND PROCAINAMIDE ON CONDUCTION OF EARLY AND LATE PREMATURE BEATS IN THE NORMAL CANINE ATRIA

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Severe hypothermia or a high serum concentration of either quinidine or procainamide increases refractoriness and slows conduction. However, in the normal heart, at moderate concentrations it is not known which effect predominates, or whether further depression of conduction of early cycle premature beats occurs. In order to determine if these interventions have similar effects on conduction when a similar lengthening of refractory period is achieved and, in addition, if conduction of early premature beats is further depressed, we paced and recorded the in-situ Bachman Bundle in 25 open chest, adult, mongrel dogs. Strength-interval curves, conduction times and the increase in conduction time during the relative refractory period were measured.

Decreasing core temperature by 4.2±0.4°C or achieving serum concentrations of quinidine or procainamide of 4.2±1.4 and 18.5±4.5μg/ml, respectively, produced similar increases in effective refractory period (46.7± 16.3, 40.6±24.1 and 25.0±12.3 ms) without changing late diastolic threshold or conduction time in late diastole. Hypothermia, but not quinidine or procainamide, further slowed conduction of premature beats during the relative refractory period (9.7±6.7 vs 0.7±7.1 vs 1.7±1.5 ms).

In the normal canine atria, hypothermia increases refractoriness and slows conduction of early premature beats. Quinidine and procainamide prolong refractoriness without slowing conduction of either late or early cycle premature atrial beats.

PRECORDIAL MAPPING OF SIGNAL AVERAGED LATE POTENTIALS COMPARED TO XYZ LEADS

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All prior studies of late potentials (LP) recorded via signal averaging have used either bipolar XYZ leads or a single precordial lead, thus assuming a total "view" of the QRS-LP duration. We compared recordings from a bipolar XYZ lead system with a set of 24 electrodes positioned in a grid across the left precordium and referenced to the back in 8 patients with documented ventricular tachycardia and LP. All patients had old inferior infarcts and were undergoing amiodarone therapy. In 3 patients there was no difference in the longest QRS-LP duration between the XYZ and mapping leads. In 3 others at least 3 of the mapping leads had a QRS-LP duration greater than (range 11-14 msec) the XYZ leads (188 vs 199 msec, 151 vs 165 msec, and 145 vs 157 msec). The longest QRS-LP duration from the XYZ leads averaged 158±30 msec while the longest QRS-LP duration from the precordial map averaged 164±29 msec. This was a significance difference with $p<0.02$ using a paired t-test (two tail). In no case was the QRS-LP duration of the XYZ leads longer than all recordings in the precordial set. The leads with the longest durations were between the borders of the third and fifth intercostal space (horizontally) and between V_4 and V_6 (vertically). **Conclusion:** Late potentials recorded with XYZ leads (or fewer leads) may inadequately represent the total QRS-LP duration. Since LP may arise from localized regions of the heart the distance of the XYZ leads from the source may result in excessive attenuation of LP.

SIGNIFICANCE OF PERCUTANEOUS INTRACORONARY EPICARDIAL ELECTROGRAPHY DURING CORONARY ANGIOPLASTY IN MAN.

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This study investigated the significance of percutaneous intracoronary epicardial electrography (PICEE) during percutaneous transluminal coronary angioplasty (PTCA). Ten patients (pts), 6 males and 4 females averaging 56 years in age (range 38-73), while undergoing PTCA has simultaneous recording of unipolar PICEE and standard monitored ECG. A steerable guide wire was used as a unipolar epicardial electrode for PICEE and was positioned distal to the stenotic lesion. For right (4 pts) and left circumflex (2 pts) coronary artery angioplasty, Leads III, AVF, V5, & V10, while for left anterior descending (4 pts) coronary artery angioplasty, I, AVL, V5, & V10 were monitored. Changes in surface ECGs were compared with PICEE at control, during inflation and after deflation of the angioplasty balloon. There were no significant changes in amplitude of the R-wave or QRS duration in standard ECGs or PICEE during inflation and deflation of the balloon. Most dramatic changes of acute myocardial ischemia (ST-T changes) during balloon inflation were observed in PICEE. PICEE showed ST elevation, (range 0.1-2.6 mV) in 3 pts, ST depression (range 0.3-3.4 mV) in 2 pts while there were no changes in standard ECGs. PICEE also demonstrated ischemic T-wave changed during balloon inflation in 4 of 10 pts. Overall, PICEE demonstrated ST-T changes of ischemia in 6 of 10 pts while standard ECG showed changes only in 1 pt. In conclusion, this study indicates that during PTCA, PICEE is more sensitive in demonstrating acute reversible myocardial ischemia than standard monitored leads and can be applied routinely.

FOCAL Tc99m PYROPHOSPHATE UPTAKE IN DOGS FOLLOWING CATHETER SHOCK; LOCALIZATION BY EPICARDIAL SCINTI-PROBE MAPPING.

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To study the feasibility of radionuclide labelling after catheter shock (CS), we correlated Tc99m pyrophosphate (PYP) uptake and histologic damage following CS.

Unipolar 25 Joule CS were given once each in the RV and LV of 5 dogs. Immediately after CS 30mBq/Kg of Tc99mPYP was injected followed by gamma-camera imaging 2 hours later. After median sternotomy, a specially constructed epicardial scintillation probe was used to measure myocardial radioactivity. Ex-vivo images were then obtained and followed by sectioning of the hearts from base to apex. Images of the slices applied directly to the collimator face were obtained and areas of increased uptake examined histologically.

External imaging showed focal activity in the RV in 2 dogs and the LV in 4 of 5 dogs. Following sternotomy, external inspection of the heart showed focal hemorrhage of the LV in 3 dogs and of the RV in 2 dogs. Epicardial probe mapping showed a focal area of uptake in the RV of 3 dogs and in the LV of all 5 dogs. Ex-vivo images showed focal areas of uptake in both the RV and LV in all hearts. These areas of uptake corresponded directly to the areas predicted by probe map and necrosis observed histologically.

We conclude that focal uptake of Tc99mPYP reliably follows CS and can often be visualized using standard gamma camera techniques. This focal uptake of Tc99mPYP can be localized using an epicardial scinti-probe and correlates exactly to the area of necrosis induced by CS. This technique may prove useful in locating arrhythmogenic foci in man by combining catheter mapping, low energy CS, and intraoperative scinti-probe mapping.

REVERSE DELTA WAVE FOR PREDICTION OF VENTRICULAR FIBRILLATION DURING RIGHT CORONARY INJECTIONS

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In a prospective study 22 episodes of ventricular fibrillation (VF) occurred during coronary angiography over three years. In 20 cases ECG lead I was recorded initially and just before the onset of VF. In four cases VF followed left coronary injection of contrast medium and in 16, injection of the right coronary artery or right aorto-coronary graft. In all but one of these, the development of a characteristic ECG sign was observed before the onset of VF. This consists of an S-wave having a sharp downstroke and a slurred upstroke with a width of at least 100 mS. The pattern resembles the delta wave of Wolff-Parkinson-White syndrome, but inverted and reversed. In eight cases the reverse delta wave was the only abnormality preceding VF, in one case there were also frequent coupled ventricular extrasystoles, in three cases there were sinus pauses and in three cases the onset of VF was obscured by artefact. An analysis of 50 unselected coronary angiograms with similar age and sex distribution and severity of coronary disease showed the occurrence of the reverse delta wave in only two cases, in both of which S-waves of at least 40 mS width were present in the initial ECG. A lesser version of the pattern with duration of 40-80 mS was recorded transiently following RCA injections in 31 cases. The reverse delta wave of at least 100 mS duration, suggesting delayed depolarisation of part of the ventricular myocardium to the right side, possibly the pulmonary conus, was thus a consistent and specific indicator of impending VF occurring, as the great majority did, during right coronary angiography.

ENTRAINMENT OF HUMAN ATRIAL FLUTTER LOCALIZES THE AREA OF SLOW CONDUCTION IN THE INFERIOR RIGHT ATRIUM

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A reentrant tachyarrhythmia usually requires an area of slow conduction to be perpetuated. We studied 9 patients (pts) with spontaneous atrial flutter (AFl), mean cycle length (CL) of 243±30 ms, to determine if slow conduction is a part of the reentry loop. Multipolar electrode catheters were placed in the high right atrium (HRA), low lateral right atrium (LRA), coronary sinus (CS) and His bundle positions. Rapid atrial pacing (RAP) was used to entrain AFl and thereby, to localize an area of slow conduction. An activation map was obtained during AFl from 30 RA sites. During AFl, the activation sequence proceeded from HRA to LRA to CS to His in all pts. During RAP from HRA, constant atrial fusion except for the last captured beat (i.e. entrainment) was demonstrated. Entrainment of AFl from the HRA at a mean RAP CL of 199±10 ms demonstrated the same atrial activation sequence to LRA and CS as during AFl, with conduction times from the stimulus to LRA and stimulus to CS of 111±48 ms (7 pts) and 223±61 ms (9 pts) respectively. In contrast, although RAP (mean CL 207±16 ms) from CS captured all atrial sites, it demonstrated none of the entrainment criteria (concealed entrainment) and did not change the ECG flutter wave morphology. This indicates that CS pacing orthodromically captures the reentry loop distal to the area of slow conduction, with the wave front proceeding from His to HRA to LRA (mean stimulus to His, to HRA, and to LRA intervals were: 58±30 ms [3 pts], 113±16 ms [3 pts] and 236±32 ms [4 pts], respectively). These data demonstrate the presence of an area of slow conduction in the inferior RA and correlate with the right atrial activation map.

PAROXYSMAL SINUS TACHYCARDIA: FURTHER EXPERIENCE WITH SUBTOTAL RIGHT ATRIAL EXCLUSION SUGGESTING DIFFUSE ATRIAL DISEASE.

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We previously reported that inappropriate paroxysmal sinus tachycardia may be treated by surgical exclusion of the sinus node. However, further experience has modified our approach. Three women presented with paroxysmal symptoms related to documented sinus tachycardia with rates up to 180/min at rest. Prior ineffective therapy included digoxin, beta-blocker, verapamil, quinidine and amiodarone. Electrophysiologic studies were normal except for a mean intrinsic heart rate of 115/min. Intraoperative mapping showed atrial activation to originate in the region of the sinus node. One week postoperatively, patients (pts) had junctional and low left atrial rhythms with a mean resting rate of 87.7/min and a peak exercise rate of 121.7/min. There were no arrhythmias one week postoperatively. During a mean followup of 20.3 months, 2 pts had paroxysmal atrial fibrillation; 2 pts had symptomatic bradycardias requiring permanent pacemaker implantation; 1 pt had exercise induced ectopic atrial tachycardia at a rate of 200/min. All pts require pharmacologic therapy. Evidence for a diffuse abnormality of automaticity includes: high intrinsic rate reflecting sinus node abnormality; high junctional escape rate; ectopic atrial tachycardia; marked bradycardia; and atrial fibrillation. Thus, inappropriate sinus tachycardia may be a manifestation of diffuse electrical disease of the atria, and sinus node exclusion alone is inadequate therapy.

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RELATIONSHIP BETWEEN LATEST ACTIVATION IN SINUS RHYTHM(SR) AND ONSET OF VENTRICULAR TACHYCARDIA(VT)

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In patients (pts) with ischemic heart disease, latest activation in SR should represent areas of slowed conduction in myocardial scarring, necessary for conduction block and reentrant pathways. If this were associated with site of onset of VT, mapping during SR could be used to direct surgical ablation. We thus recorded VT and SR during map-guided surgery in 8 pts with previous myocardial infarction. Discrete LV aneurysms were present in 6 pts. An automatic mapping system enabled simultaneous endocardial (ENDO) and epicardial (EPI) recordings from a total of 220 unipolar electrodes. Using a fixed matrix, the earliest onset of VT was marked and the last 24 msecs of activation in SR was delineated. The mean QRS during SR was prolonged at 149 msecs because of LBBB in 7 pts while ENDO activation was correspondingly prolonged with a mean of 124 msecs. No EPI or ENDO electrograms extended beyond the surface QRS. Of 20 episodes of VT recorded, the earliest onset of VT occurred on the ENDO in 18 episodes, and on the EPI in 2. The site of onset of VT was located either on the border of latest activation in SR or within a surrounding perimeter no wider than 2 cms, in 85% of episodes (17 of 20). A further 2 episodes of VT (in 1 pt) had earliest onset on the border of a large LV aneurysm but were remote from the latest detectable activation in SR. The earliest onset of VT in our pts was thus closely associated with latest activation in SR and may represent the exit point of the reentrant pathway. With improved understanding of reentrant mechanisms in human VT, our approach to surgical ablation of VT may ultimately be modified by mapping of latest activation in SR.

THE INCIDENCE AND SIGNIFICANCE OF DELAYED AND FRACTIONATED RIGHT VENTRICULAR ELECTRICAL ACTIVITY IN MAN.

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Abnormal (AB) (i.e delayed and fractionated) LV electrograms (E's) have been reported in patients (pts) with LV aneurysms and sustained (sust) ventricular tachycardia (VT). Although most electrophysiologic studies are performed in the RV, little is known of the incidence and significance of Ab-RVE's. We prospectively evaluated RVE's in 50 pts (54 ± 15 yrs; ± S.D.) during RV catheter (5mm spacing) mapping of 6-10 RV sites. 20/50 pts had sust VT, 20/50 pts had non-sust VT and 10/50 pts had no VT. Results: Two types of Ab-RVE's were seen: Type I-early potentials (duration (d) = 69 ± 75 ms; peak Voltage (V) = 114 ± 108 μv) occurring immediately after the end of the QRS. Type II-late potentials (d = 168 ± 110 ms; V = 113 ± 65 μv) occurring 261 ± 109 ms after the end of the QRS. Ab-RVE's were seen in 17/50 pts (34%) of which 10/17 pts (59%) had sust VT; 6/17 pts (35%) had non-sust VT and 1/17 pts (6%) had no VT. Eleven of seventeen pts had type I, 14 had Type II and 8 had both. Ab-RVE's occurred at the RV apical septum in 65% and RV basal-septum in 35%. Fractionated Type II E's were more frequent (90% vs 17%, p<.003) and longer (214 ± 99 vs 64 ± 40 ms, p<.02) in pts with sust. VT than in non-sust VT. Fractionated Type II E's occurred in 9/20 pts with sust VT, but in only 1/30 pts without sust VT and had a sensitivity of 45% a specificity of 97% and positive predictive value of 90% in separating pts with sust VT from those without. Bridging of RVE's was noted in only 3 pts during VT. Conclusions: (1) Ab-RVE's are often observed in pts with VT but rarely in pts without VT. (2) Fractionated Type II RVE's are seen mostly in pts with sust VT and reflect desynchronized RV-septal electrical activity. (3) Fractionated Type II RVE's lack sensitivity but have a high specificity and positive predictive value for sust VT. (4) Bridging of RVE's during VT is rare impling remote site of VT origin.

REPRODUCIBILITY OF THE RESULTS OF PROGRAMMED VENTRICULAR STIMULATION EARLY AND LATE AFTER ACUTE MYOCARDIAL INFARCTION

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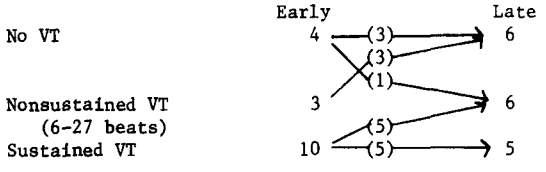
The significance and long term reproducibility of the results of programmed ventricular stimulation(PVS) in patients early after acute myocardial infarction(MI) is not known. Reproducibility of the response to PVS, using up to 2 extrastimuli during pacing, and up to 3 during sinus rhythm, at the RV apex, was investigated in 17 patients. PVS was performed early, 13±4 days(mean ± SD, range 8-25 days) after acute MI treated with thrombolytic therapy, and late, 10±7 months (range 3-29 months) after MI, using the same PVS protocol. Ventricular tachycardia (VT) (cycle length 212±39 ms) was induced early in 13 of 17, and was treated by cardioversion in 9. VT (cycle length 230 ± 49 ms) was induced late in 11 of 17. The results are shown below:



In this select group of patients studied early and late post MI, early inducible nonsustained VT was not reproduced late. All the patients with sustained VT induced late had sustained VT induced early; however, inducible sustained VT persisted in only 50%. Reproducibility of the electrophysiologic abnormalities identified early after MI by PVS is therefore highly variable.

PSEUDO PROLONGATION OF THE HIS VENTRICULAR INTERVAL IN ANTEROSEPTAL INFARCTION.

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The His-ventricular (HV) interval represents conduction time from the proximal His-bundle to the ventricular myocardium. It is traditionally taken as the interval from the beginning of the His-bundle deflection to the earliest onset of ventricular activation recorded from surface ECG leads or local RV electrograms at the atrioventricular (AV) junction. We have analyzed LV endocardial catheter mapping data during sinus rhythm in 25 patients (pts) with anteroseptal infarction (AMI) to determine if pre-systolic activity was present and hence whether standard measurements using the surface QRS overestimated the HV interval. The mean HV interval measured in the traditional manner was 57±9 msec. Presystolic activity was recorded in 22/25 (88%) of pts and was recorded a mean of 15±9 msec prior to the onset of the surface QRS complex. This activity was recorded from the LV septum in 18 pts and from the anterior free wall in 4 pts. When this LV activity was considered the earliest ventricular activity, the measured HV interval shortened from 57±9 msec to 42±14 msec ($p<.001$). We conclude: 1) Presystolic low amplitude electrical activity can be recorded from the LV septum or anterior wall in the majority of pts with AMI. 2) Pseudo prolongation of the HV interval results when the onset of ventricular activity was measured from AV junction or the surface QRS in pts with AMI. 3) This data suggests that prolonged HV interval in pts with AMI may be due to failure to record low amplitude ventricular activity rather than slow conduction in the His-purkinje system. This may have importance in the management of syncope in pts with bifascicular block and AMI.

EFFECTS OF DIFFERENT PACING PROTOCOLS IN PATIENTS AFTER ACUTE MYOCARDIAL INFARCTION

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We have demonstrated that patients (pts) with inducible (Protocol I, see below) ventricular tachycardia (VT) after acute myocardial infarction (AMI) are prone to sudden death. This prospective study compared the effects of two separate protocols of programmed stimulation applied in random order to 81 pts (aged 37-70 years) 7-15 days following AMI. Protocol I comprised stimulation at the right ventricular apex (RVA) and outflow tract with 1 and 2 extrastimuli at twice diastolic current threshold and at 20 mA. Protocol II comprised 1, 2, 3, 4 & 5 extrastimuli at twice diastolic threshold at the RVA. End points were ventricular fibrillation (VF) and sustained VT.

INDUCIBLE RHYTHM	PROTOCOL I	PROTOCOL II
VT CL ≥ 200 ms	13 (16%)	23 (28%)
VT CL < 200 ms	7 (9%)	20 (25%)
VF	10 (12%)	26 (32%)
No VT/VF	51 (63%)	12 (15%)

We conclude 1. The more aggressive Protocol II produced not only more slow VT, but also more VF and fast VT, than Protocol I. 2. Rapid VT and VF may be false positive responses to aggressive stimulation, and their clinical significance remains to be determined.

SIGNIFICANT VARIABILITY IN THE INDUCTION OF VENTRICULAR TACHYCARDIA.

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Electrophysiologic studies (EPS) to test drug efficacy for treatment of sustained ventricular tachycardia (VT) without serial control studies assume a high reproducibility of VT induction and required number of extrastimuli (#ES). To test these assumptions, the results of 2 control studies at the right ventricular apex (EPS1 and EPS2) within 72 hours, were compared in 52 consecutive patients (pts) with prior infarction and documented spontaneous sustained VT (43 pts) or VF (9 pts). Sustained monomorphic VT (≥30 secs) was induced in 43 pts (83%) during EPS1 and in 44 pts (85%) during EPS2. VT was induced at both EPS in 40 pts and at neither EPS in 5 pts (concordant result 87%). VT was induced at only one EPS in 7 pts: 3 at EPS1, 4 at EPS2 (discordant result 13%). Of the 40 pts with VT inducible at both EPS, the change in #ES required to induce VT from EPS1 to EPS2 was as follows:

	1 ES	2 ES	3 ES	4 ES	TOTAL
EPS 1	5	15	15	5	40
Same #ES	1	6	5	4	16
Fewer #ES	0	1	6	1	8(20%)
Greater #ES	4	8	4	-	16(40%)
Variability [≥1 ES]	4/5	9/15	10/15	1/5	24/40(60%)

Major variability [≥2ES (7 pts) or induced ↔ non-induced sustained VT (7 pts)] occurred in 14/52 (27%) pts.
Conclusion: Significant variability exists in inducibility of sustained VT from day to day. Serial control EPS are necessary to minimize the chance that intrinsic variability would mimic a beneficial or detrimental effect when testing drugs.

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ACUTE ANTIARRHYTHMIC DRUG EFFICACY IS INDEPENDENTLY RELATED TO LEFT VENTRICULAR FUNCTION.

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To evaluate the relation between antiarrhythmic drug efficacy and LV function we performed 717 electrophysiologic studies (EPS) in 251 patients (pts) with inducible sustained (>30 sec) ventricular tachyarrhythmias (VTA). A standard EPS protocol (3 extrastimuli) was used to test: procainamide and quinidine alone; mexiletine alone or in combination with procainamide or quinidine; amiodarone alone or in combination with procainamide or quinidine; flecainide, indecainide or other agents. Antiarrhythmic success was defined as inability to initiate sustained VTA. The median ejection fraction (EF) was 30%; thus pts were grouped by radionuclide EF as either $<$ or $\geq$ EF of 30%. Success was more frequent in pts with EF$\geq$30% (n=117) than in pts with EF$<$30% (n=134) (68% vs 37%, p$<$.001). Differences between the two groups could not be explained by differences in drug dose, blood levels, or type of heart disease (p=NS). We conclude that: acute response to antiarrhythmic drugs is related to LV function per se or to other underlying pathophysiologic mechanisms of which EF may be a marker.

MECHANISM AND ORIGIN OF VENTRICULAR ARRHYTHMIAS FOLLOWING ELECTRICAL CATHETER ABLATION.

Richard N. Hauer, M.D., Etienne O. Robles de Medina, M.D., F.A.C.C., Cornelius Borst, M.D., University Hospital, Utrecht, The Netherlands.

A high incidence of ventricular tachycardias(VT) following ventricular electrical catheter ablation in dogs was shown in previous studies. Mechanism and origin of these VT were studied in 12 beagles treated with single R wave triggered shocks with 30(4 dogs), 80(2 dogs) or 250 J (6 dogs) delivered to the endocardial ventricular wall (5 dogs right ventricular, 7 dogs left ventricular) using a catheter electrode as the cathode and a back paddle as the anode. Programmed electrical stimulation(PES) from or near the ablation site(AS) at twice diastolic threshold, using at least 2 cycle lengths and 1, 2 and 3 extrastimuli and burst pacing, was performed prior to the shock and within 1 hour thereafter. PES was repeated after 1 week (10 dogs) or 1 month (2 dogs). In each dog many spontaneous episodes of monomorphic VT occurred within the first hour following the shock. These VT originated from the AS as determined by recording of early negative deflections in the unipolar electrograms derived from the AS during VT. In addition, QRS morphology(3-6 leads) was identical to preablation QRS during pacing at the AS. High incidence of VT persisted during the first 3 days after the shock as shown by extended Holter monitoring and was independent of delivered energy. However, VT was never inducible with PES. Our results indicate:1. High incidence of postablation VT independent of delivered electrical energy. 2. Early postablation VT originates from the AS and the mechanism is most compatible with abnormal automaticity. 3. No evidence that the ablation lesion creates appropriate circumstances for early or late reentry with shocks in the 30-250 J energy range.

DO POLYMORPHIC VENTRICULAR ARRHYTHMIAS INITIATED IN POST MI PATIENTS DIFFER FROM THOSE INITIATED IN THE STRUCTURALLY NORMAL HEART?

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Polymorphic ventricular arrhythmias (PVA) initiated by programmed stimulation may be clinically important or nonspecific. To determine if PVA initiated in pts with spontaneous sustained ventricular arrhythmias (VA) differ from nonspecific PVA, the incidence, and characteristics of > 5 beats of PVA were compared in 32 pts with structurally normal hearts without spontaneous VA (NH) and 36 pts with sustained VA late after myocardial infarction (MI). Pts received 1 to 4 extrastimuli during sinus rhythm and right ventricular pacing at 3 cycle lengths. Comparing the same steps in the stimulation protocol there was no difference in the risk of initiation of a PVA between MI and NH pts (51% vs 38% with up to 2 stimuli, p NS). PVA were initiated by the same number of stimuli (2.3 $\pm$ 0.5 vs 2.6 $\pm$ 0.9, p NS) with the same prematurity (222 $\pm$ 37 vs 215 $\pm$ 37 msec, p NS) in both groups. A mean PVA cycle length > 250 msec or a coupling interval of the first PVA beat to the last stimulus > 320 msec occured in 44% of PVA in MI pts but only 1 (6%) pt in the NH group (p < .02).

Conclusion: Most PVA initiated in pts with VA after MI are indistinguishable in method of initiation and cycle length from PVAs induced in structurally normal hearts suggesting that they are nonspecific.

HYPOKALEMIA IN PATIENTS WITH VENTRICULAR TACHYCARDIA.

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Pts resuscitated from an episode of sudden cardiac death (SD) have been found to be hypokalemic at the time of resuscitation. Several centers suggest that pts found to be hypokalemic at the time of SD are at low risk of recurrence and need no therapy other than correction of the hypokalemia. The purpose of this study was to evaluate whether low plasma potassium (pK) may be a result of ventricular tachycardia (VT) or fibrillaiton (VF). In a group of 9 pts with VT or VF baseline pK and epinephrine was done prior to electrophysiologic testing (EP). Epinephrine and pK were repeated at 2 minutes and 15 minutes after induction of sustained ventricular tachycardia or fibrillation. EP resulted in 15 episodes of sustained VT or VF. In 6 episodes (group I) pK fell by 0.3mEq or more. Baseline pK was 4.1±0.4 which decreased to 3.6±0.3mEq/L at 2 minutes and 3.6±0.4 at 15 minutes following VT or VF ($p<0.002$). In 9 episodes of VT or VF (group II) pK fell by 0.2 mEq/L or less. Serum epinephrine rose in group I (98.7±103 baseline to 135±36.5 (NS)) and group II (83.6± 42 to 111.0±47(NS)). Duration of VT or VF was 419±689 secs (group I) vs 132±274 (group II (NS)). One pt in group I was on non-selective B blockers vs 4 in group II.

We conclude that hypokalemia is a frequent result of sustained ventricular arrhythmias and that hypokalemia found at the time of resuscitation should not be thought of as a cause of the arrhythmia but possible as a result of it. Hypokalemia may be mediated by a rise in catecholamines.

Tuesday, March 11, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 3:00PM–4:00PM
Hall D, Georgia World Congress Center
Electrophysiology—Clinical

OBSERVATIONS WITH CLOSED-CHEST CATHETER ABLATION OF CANINE VENTRICULAR ENDOMYOCARDIUM WITH RADIOFREQUENCY ENERGY.

Shoei K. Huang, M.D., F.A.C.C., Keith Wharton, B.S., Anna R. Graham, M.D., Robert H. Hoyt, M.D., Frank I. Marcus, M.D., F.A.C.C., University of Arizona, Tucson, Arizona.

Catheter ablation of ventricular arrhythmias using DC energy has disadvantages. We assessed the efficacy and safety of closed-chest catheter ablation of ventricular endomyocardium using radiofrequency (RF) energy in 5 dogs with microbipolar standard RF output (750 KHz). RF energy was delivered between the tip electrode of a standard 7F USCI tripolar catheter (10mm spacing) in the left ventricle and an external patch electrode on the left lateral chest wall. RF energy was delivered to 3 LV sites with different energy settings for the individual sites; 10W X 10 sec to the septum, 20W X 10 sec to the posterior wall and 30W X 10 sec to the apex. Twenty-four hour Holter recordings were obtained, starting immediately after the procedure. Dogs were sacrificed on the 5th day. Pathology showed well delineated oblong whitish lesions at the ablation sites. The mean length of necrosis was 8.2mm, range 4-15mm; mean width 4.9mm, range 2-9mm; and mean depth 4.8mm, range 2-7mm. Microscopic findings consisted of circumscribed areas of necrosis surrounded by a zone of fibroblastic and mononuclear proliferation and small vacuolation. Occasionaly a thin layer of endocardial thrombus at the ablation site was seen. Creatine phosphokinase ranged from 8590 to 11090 IU/L with MB fraction of 3-12%. Ventricular arrhythmias were not observed during and 24 hrs after ablation. There was no damage to the electrode catheters. Conclusion: Catheter ablation of ventricular endomyocardium with RF energy produced well circumscribed injury and did not induce ventricular arrhythmias. This technique has potential utility for catheter ablation of ventricular arrhythmias.

CHARACTERISATION OF CATHETER ABLATION WITH HIGH SPEED CINEMATOGRAPHY

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Although catheter ablation is gaining acceptance as a treatment for arrhythmias, the physical events associated with electrical discharge that result in ablation of tissue remain obscure. To investigate this, we used high-speed cinematography at 4000 frames/sec to record 300J discharges in a transparent chamber of normal saline. Discharges were of a damped sinusoid waveform. The electrodes included a 10 x 8 cm steel plate and the distal pole of USCI electrode catheters. Unipolar cathodal discharges between catheter and plate produced a blue gaseous sphere (GS) which reached a maximum size of 25 mm radium in 4 msec and collapsed with a series of implosions over 6 msec without visible gaseous residium. During the initial formation phase of GS, a spark was evident between the electrode and the perimeter of the sphere. Phenolphthalein dye indicated a strong alkaline pH around the catheter. No visible changes occurred at the anodal plate. Changes at the catheter electrode were indifferent to the position of the plate electrode. Anodal discharges at the catheter resulted in similar events except the GS was yellowish and no alkalinity was observed. Bipolar discharges between catheters 8 cm apart resulted in convergence of the implosive phases. Unipolar catheter discharges from the LV apex of sheep hearts resulted in violent movements of the LV wall by the GS, and perforation by the spark. These observations suggest catheter ablation may achieve its effect by a combination of barotrauma, fulguration and chemical cautery. The configuration of these effects appears indifferent to the position of the electrode plate.

HAEMATOLOGICAL EFFECTS OF THE ABLATION TECHNIQUE; A COMPARISON BETWEEN ANODAL AND CATHODAL DELIVERY

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Guy's Hospital, London, England

Ablation of atrioventricular conduction is now widely accepted in the management of supraventricular arrhythmias. Reports of high temperatures, high pressures and gas production suggest that there may be adverse effects on the blood, the electrode and the cardiovascular system. This investigation, using samples of fresh, heparinised pig's blood, has measured the haemolytic damage, the liberated gas volume and composition, and electrode erosion. The blood was tested in a litre tank at room temperature. Impulses of 10 joules to 400 joules were applied to new USCI 6F bipolar pacing electrodes using negative polarities. (Anodal energy deliveries could not be used above 200J because the pressures generated destroyed the gas collection apparatus). Voltage and current waveforms were recorded to assess the similarity of the tank to the clinical situation. The volume of gas liberated with a cathodal electrode was 0.43 ul/J up to 50J and 0.19 ul/J above 100J. It was composed predominately of hydrogen and nitrogen, with carbon dioxide and oxygen. Using a positive electrode the gas volume was linearly related to energy at 4.25 ul/J up to 200J. In addition the gas also contained carbon monoxide. The haemolysis was directly proportional to impulse energy for both cathodal and anodal electrodes, being 1.35 ul/J and 4.53 ul/J, respectively. After 48,000J electrode erosion was substantial and neutron activation analysis showed platinum losses of 2.94mg and 0.84mg. Electron microscopy showed very different electrode surface patterns for the two types of energy delivery. The results suggest that lower energies and cathodal energy delivery is more appropriate for the clinical endocardial ablation procedure.

PATHOLOGICAL AND ELECTROPHYSIOLOGICAL OBSERVATIONS OF CHRONIC ATRIOVENTRICULAR BLOCK INDUCED BY CLOSED-CHEST CATHETER ABLATION WITH RADIOFREQUENCY ENERGY.

Shoei K. Huang, M.D., F.A.C.C., Saroja Bharati, M.D., F.A.C.C., Maurice Lev, M.D., F.A.C.C., Frank I. Marcus, M.D., F.A.C.C., University of Arizona, Tucson, Arizona.

DC energy has been used to induce atrioventricular block (AVB) but this type of energy is not ideally suited for this purpose. Therefore, we induced chronic AVB by closed-chest catheter ablation of the AV junction with radiofrequency (RF) energy in the dog. The animals were observed for 2 months to determine if the ablation was permanent to define the chronic pathology and the site of AV block. Complete AVB was successfully achieved in 4 dogs with a microbipolar standard RF output (750 KHz) delivered between the tip electrode of a standard 7F USCI catheter and an external patch electrode on the left lateral chest wall. Three dogs had persistent complete AVB, the other had persistant 2:1 AVB. Permanent pacemakers were implanted in the 3 animals with complete AVB. His bundle recordings were performed immediately after ablation and at 2 months. Results: The site of block was above the His bundle in all 4 animals. The degree of injury was graded on a scale of 0-4+. Injury was 4+ at the AV node in all 4 animals; 1-3+ at the approach to the AV node; 0-4+ at the penetrating bundle and 1+ in only 1 dog at the branching bundle. The damaged area was well delineated. The AV node was completely replaced with granulation tissue and cartilage formation. There was fatty infiltration and chronic inflammatory cells around the lesions. Neither perforation, hemorrhage or vacuolation was seen in the adjacent area. Thrombi were not present. Conclusion: RF energy can achieve chronic AV block and produce well circumscribed pathological lesions.

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INDUCTION OF AV NODAL (AVN) DELAYS AND BLOCK BY A THERMAL CATHETER TECHNIQUE: ACUTE AND CHRONIC STUDIES.

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In 20 mongrel dogs anaesthetized with Nembutal, a specially designed thermal electrode catheter (7F) was introduced via a femoral vein and positioned at the His bundle (BH) and AVN region for intracardiac recordings, localization, and delivery of thermal energy. Autonomic blockade was produced with IV Inderal (5mg) and atropine (1mg). Thermal energy (9-16 watts) was delivered for 2-6 second durations to induce graded A-H prolongation in 10, 2° A-H block in 2, and 3° A-H block in 8. Results in dogs with A-H prolongation are tabulated below:

	CONTROL	POST PROCEDURE
P-P	380-630, mean 499*	300-700, mean 511*
P-R	110-125, mean 116*	125-190, mean 158*
A-H	55-75, mean 67*	70-140, mean 107*
APCL	190-320, mean 249*	170-410, mean 268*
ERP AVN	<140-250, mean 184*	<160-370, mean 217*

APCL = Atrial pacing cycle length for 2° A-H block.
* = msec. ERP = Effective refractory period.

In each dog, H-V time (35-40msec), QRS duration (60msec), and morphology remained unchanged throughout. In dogs with 3° A-H block, escape BH rhythm (CL=1600-2000msec) showed H-V time and QRS similar to control. Repeat studies at 3-7 month intervals documented the persistence of induced A-H delays, 2° and 3° block without regression. In conclusion, persistent and graduated AVN delays can be induced via a catheter technique using thermal energy. The latter technique is preferable to our previously described laser catheter technique, as the instrumentation is simpler and economical.

COMPARISON OF THE DEFIBRILLATION THRESHOLD AND THE UPPER LIMIT OF VENTRICULAR VULNERABILITY

Peng-Sheng Chen, M.D., Nitaro Shibata, M.D., Ellen G. Dixon, M.S., Michael J. Fine, B.S., and Raymond E. Ideker, M.D., Ph.D. Duke University Medical Center, Durham, NC

We have shown that unsuccessful defibrillation shocks $\geq$ 1 J applied to the epicardium extinguish all cardiac activations for 64±22 SD ms, yet fail to defibrillate because VF is reinitiated following the shock. Since VF is sufficiently complex so that there are always some cells in their repolarizing phase, this finding raises the hypothesis that unsuccessful shocks $\geq$ 1 J fail because they reinitiate VF by stimulating portions of myocardium in their vulnerable period. A corollary of this hypothesis is that the energy of the strongest shock that can induce VF during the vulnerable period of regular rhythm (the upper limit of vulnerability) should be correlated with the defibrillation threshold (DFT) energy. To examine this relationship, we studied 14 open chest dogs with epicardial defibrillation electrodes at the ventricular apex and either the RA or LA. We determined the upper limit of ventricular vulnerability by giving shocks of various energy during the vulnerable period of the repolarization phase of paced rhythm. We also determined the DFT. In all dogs there was an upper limit to the shock strength that induced VF during the vulnerable period. This upper limit of ventricular vulnerability was slightly lower than the DFT. The correlation coefficient between the two was highly significant ($r=0.92$, $p<0.0001$ for apex and RA combination, and $r=0.89$, $p<0.005$ for apex and LA combination). These results are consistent with the hypothesis that successful defibrillation with epicardial electrodes requires a shock strength that reaches or exceeds the upper limit of ventricular vulnerability and that shocks slightly lower than the DFT fail because they reinitiate VF by stimulating portions of myocardium in their vulnerable period.

EXERCISE CAPACITY AND HEART RHYTHM FOLLOWING TRANSVENOUS FULGURATION OF ATRIOVENTRICULAR CONDUCTION.

Peter Schofield, MRCP., Robert Bowes, MRCP., David Bennett, M.D., MRCP. Wythenshawe Hospital, Manchester, England.

24 patients, aged 19-67 years, were studied 4-36 months after transvenous fulguration of the atrioventricular (AV) junction in order to assess exercise capacity and spontaneous heart rhythm. 15 patients had had atrioventricular reentrant tachycardia and 9 patients, 4 with mitral valve disease and 5 with the brady-tachy syndrome, had had an uncontrollable ventricular response to atrial fibrillation or flutter. 1-3 DC shocks of 200-400 joules were delivered via a His bundle electrode in each case. After fulguration, 17 patients had complete and 5 partial AV block. In 2 patients sinus rhythm was maintained via an accessory AV pathway. Though all patients were free of palpitation after the procedure, 10 developed exertional dyspnoea and 2 patients' pre-existing dyspnoea worsened. 23 patients underwent exercise testing during ventricular demand pacing at 60 or 70 bpm using the Bruce protocol. Exercise time was reduced to 45% ± 23% (mean ± SD) of the predicted value for their age and sex. In 6 patients with complete AV block, there was an increase in ventricular rate during exercise. In 3 patients with partial heart block, the degree of AV block increased on exercise. The 13 patients with rate responsive pacemakers demonstrated a significantly better but still impaired exercise capacity during physiological pacing (67% ± 24%) as compared with their performance during fixed rate pacing (41% ± 18%) ($p<0.001$). We conclude that though the procedure is successful in controlling tachycardia it may cause a reduction in exercise capacity. Most patients remain in complete AV block after the procedure and, in contrast to the practice as described in early publications, would benefit from "physiological" pacing though even with this mode exercise capacity is likely to be abnormal.

TRANSMYOCARDIAL ELECTRICAL IMPEDANCE: RELATIONSHIP TO CANINE DEFIBRILLATION THRESHOLDS.

Rehan Mahmud, MD, FACC, Jeffrey Milsap, Anita Krebs, RN, Patrick Tchou, MD, Michael H. Lehmann, MD, FACC, John Dongas, MD, Stephen T. Denker, MD, FACC, Masood Akhtar, MD, FACC, Univ. of WI Mt. Sinai Med Center, Milwaukee, WI.

Implantation of automatic internal defibrillators (AID, requires lead placement at sites demonstrating low defibrillation thresholds (DFT). It was hypothesized that if the transmyocardial impedance (TMZ) was primarily resistive, it may be possible to predict the optimal AID leads location by determining the sites with low TMZ; as reported for external cardioversion. In 10 open chested dogs (wt $\geq$ 20 kg), 6cm^2 AID patches were placed on left ventricle and right ventricle or atrium simulating placement during AID implants. Ventricular fibrillation was induced using AC current. DFT's were determined using a damped sine wave discharge of 5 msec duration. Voltage (V) and current (I) were displayed simultaneously on an oscilloscope using a 44:1 V attenuator and a low resistance shunt. TMZ was determined at the peak V and I waveforms. In 2 control dogs, phase relationship of V and I was determined by displaying V versus I in an analog fashion using single ended measurements (Lissajous figure). Results: 1) In the 2 control dogs using energies varying from 2-50 joules (J) the V and I were linearly related (r= .99) suggesting a primarily resistive TMZ. 2). In the study group (8 dogs, 24 sites), the mean DFT was 11 ± 6 J (range 3.9 - 13J), and TMZ was 68 ± 13 ohms (range 45.6 - 94.5 ohms). Coefficent of correlation between DFT's and TMZ:r = -.34. Conclusions: Despite the primarily resistive character of the TMZ, there was a poor correlation between DFT's and TMZ in the canine model. Our data suggest that determination of TMZ may not have the predictive value that has been reported for transthoracic impedance during external cardioversion.

SURGICAL INTERRUPTION OF NODOVENTRICULAR MAHAIM FIBERS WITH PRESERVATION OF NORMAL A-V CONDUCTION. John J. Gallagher, MD, FACC, Jay G. Selle, MD, Will C. Sealy, MD, John M. Fedor, MD, FACC, Robert H. Svenson, MD, FACC, Samuel H. Zimmern, MD, FACC. Sanger Clinic PA, Charlotte, North Carolina and James C. Cox, MD, FACC, Barnes Hospital, St. Louis, Missouri.

Nodoventricular (NV) Mahaim fibers have been shown to be responsible for some examples of supraventricular tachycardia (SVT) in man. Because of their intimate relationship to the atrioventricular (A-V) node, these fibers have been thought to be unapproachable by ablative techniques because of the risk of complete A-V block. Successful interruption of an NV fiber has now been achieved in 3 patients without damage to the A-V node-His bundle.

Three patients aged 18, 25, and 33 years presented with recurring SVT. All had preoperative and intraoperative confirmation of accessory A-V pathways in the right A-V groove and posterior septal (PS) space in addition to an NV fiber. Two of the three had coexisting Ebstein's anomaly. The boundaries of the pyramidal space and the right A-V groove were dissected thoroughly after identifying the location of the His bundle. Particular attention was given to dissection of the posterior limit of the atrial septum, but the septum itself was not entered. Intraoperative and postoperative studies confirmed division of all pathways including the NV fiber, with preservation of normal A-V conduction. Retrograde conduction was absent in all. All patients have remained free of preexcitation and tachycardia, with a follow-up of 3 years, 3 years and 3 months respectively.

Despite their proximity to the AV node, NV fibers may be divided by a septal dissection leaving normal conduction intact, suggesting a location at the posterior-inferior aspect of the AV node.

SURGERY FOR WOLFF-PARKINSON-WHITE SYNDROME USING A CLOSED HEART TECHNIQUE: FURTHER EXPERIENCE AND POTENTIAL LIMITATIONS. Gerard M. Guiraudon, M.D., F.A.C.C., George J. Klein, M.D., F.A.C.C., Arjun D. Sharma, M.D., F.A.C.C., University Hospital, London, Ontario, Canada.

We have described a closed heart technique for division of atrioventricular pathways (AP) in the Wolff-Parkinson-White (WPW) syndrome. The technique involves dissection and mobilization of the AV fat pad with exposure and cryoablation of the AV junction at the site of the AP.

Ninety three consecutive WPW patients with LV free wall AP (66), posteroseptal AP (16) and RV free wall (11) were operated between July 1982 and August 1985. Three patients had multiple accessory pathways and 8 had associated cardiac disease. Electrophysiological testing to determine the presence and site of the AP was performed before and after dissection of the fat pad and again after cryoablation of the AV junction.

All AP but 1 were successfully ablated with no mortality and no incident of AV block. Ninety two patients remain free of arrhythmia in the absence of drugs after a mean follow-up of 14 (1-38) months. Three patients required a second operation within the first week for recurrence of AP conduction. In 2 of these patients, AP conduction persisted after extensive dissection and exposure of the AV junction and only disappeared after cryoablation. Recurrence of AP conduction in the latter patients suggests the presence of a subendocardial pathway protected from cryoablation by the warm circulating blood pool.

We conclude that the closed heart technique is safe and efficacious. A potential limitation may be the presence of subendocardial AP which may require alternative approach at the site of the AP.

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Poster Displayed: 2:00PM–5:00PM
Author Present: 2:00PM–3:00PM
Hall D, Georgia World Congress Center
Echocardiography/Doppler

EFFECT OF INTRAVENOUS METOPROLOL ON INFARCT SIZE FOLLOWING REPERFUSION: EVALUATION USING CONTRAST ECHOCARDIOGRAPHY; Charles G. Vasey, M.D., John A. DeSanto, B.S., William F. Armstrong, M.D., F.A.C.C.; Indiana University School of Medicine, Krannert Institute of Cardiology; Indianapolis, Indiana

We studied 38 open chest dogs to assess the effect of intravenous metoprolol (Met) on the size of reperfused myocardial infarction. Myocardial contrast echocardiography (MCE) immediately, 1 and 2 hrs after coronary artery occlusion (CAO) was used to determine the area at risk. A 2 hr CAO was followed by 2 hrs of reperfusion. A pretreated group received Met .5 mg/Kg before CAO and .25 mg/Kg 1 hr after CAO. Ten dogs received Met 0.75 mg/Kg 1 hr after CAO (delay) and 10 dogs served as controls. A fourth group received identical pretreatment with Met but was then atrially paced at the baseline heart rate (pace). Reperfusion was confirmed with MCE immediately, 1 and 2 hrs after release of CAO. The corresponding LV section was stained with nitro-blue tetrazolium to determine infarct size, which was expressed as a percent of the risk area.

	% Risk	MI %	MI/Risk %	
Pretreat (n = 11)	27.6	5.7	20.7 ± 12.3	
Delay (n = 10)	29.5	7.8	28.4 ± 19.4	$p < .005$
Control (n = 10)	20.3	9.1	45.0 ± 20.9	$p < .05$
Pace (n = 7)	29.1	14.6	53.0 ± 20.0	NS

While there were no intergroup differences in blood pressure following Met, heart rate slowed in the pretreat and delay groups in comparison to both the control and pace groups ($p<.05$). We conclude that either pretreatment or delayed treatment with Met, followed by reperfusion, limits infarct size. This effect appears to depend predominantly on reduction in heart rate and presumably reduced myocardial oxygen demand following beta blockade.

EVIDENCE OF REVERSE TETHERING OF ISCHEMIC MYOCARDIUM BY INOTROPIC CHALLENGE. Andrew J. Buda, M.D., F.A.C.C., Rainer J. Zotz, M.D., and Kim P. Gallagher, Ph.D., University of Michigan, Ann Arbor, Michigan

During acute myocardial ischemia, there exists a zone of myocardial dysfunction which surrounds the central ischemic area which has been termed the functional border zone (FBZ). We hypothesized that nonischemic dysfunctional myocardium may respond to an inotropic challenge and may affect the function of the adjacent myocardium by a reverse tethering effect. To examine this, we studied 12 open-chest dogs during acute left circumflex (LCx) occlusion. Simultaneous 2D echocardiograms and radioactive microspere injections were used to create circumferential left ventricular (LV) flow-function maps at the papillary muscle level. Serial studies were performed at baseline, 15 minutes following left circumflex occlusion, and following dobutamine (Dob) infusion during LCx occlusion. Following occlusion, wall thickening decreased from 52±8% (mean ± SEM) to -5±5% ($p<.01$) in the central ischemic zone. The extent of LV dysfunction measured 170±11° while the subendocardial hypoperfusion zone was 130±9° ($p < 0.05$) resulting in a FBZ of 42±11°. Following Dob, wall thickening did not change in the central ischemic zone but increased adjacent to the FBZ ($p<0.01$) and in the normal zone ($p<0.05$) reducing the extent of the FBZ to 19±16° ($p<0.05$). Following Dob, the slope of the transition of function from nonischemic to central ischemic zones increased on the free wall border (.71±.11 to .95±.10, $p<0.02$) to a greater extent than on the septal border (-.60±.08 to -.73±.06, $p=0.07$). We conclude: (1) nonischemic myocardium adjacent to ischemic tissue responds to inotropic challenge; (2) Dob produces a significant decrease in the size of the FBZ; (3) reverse tethering can occur following inotropic intervention; (4) dynamic changes in function following inotropic intervention are greater in the lateral free wall border than in the lateral septal border of the FBZ.

MECHANICAL SEQUELAE OF SUBACUTE MYOCARDIAL INFARCTION IN THE CANINE VENTRICLE: IMPLICATIONS FOR INTERVENTIONS DESIGNED TO SALVAGE MYOCARDIUM

Robert J. Mich MD, Douglas L. Mann MD, Rodney A. Foale MD, Linda D. Gillam MD
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To assess the functional benefit of myocardial salvage, it is essential to define the natural history of mechanical dysfunction following myocardial infarction. We have reported that the circumferential extent of abnormal wall motion does not change from 6 to 72 hours. To further define regional function we examined the evolution of hypokinesis (HYPO) and dyskinesis (DYS) within the infarct zone (IZ) and border zone (BZ) in 10 closed-chest dogs at 0, 0.5, 6, 24, 48 and 72 hours following experimental myocardial infarction. Short-axis echocardiograms were obtained at the mid-papillary level. Postmortem TTC-stained slices corresponding to the echo planes were divided into: IZ = any region showing infarction; and BZ = 30^{o} on either side of IZ. The end-diastolic to end-systolic fractional radial change was assessed at 10^{o} intervals: HYPO was defined as a fractional radial change < 10% and DYS as a fractional radial change < 0%. The number of 10^{o} radians with HYPO/DYS was expressed as a % of the total. Results:

	Zone	Control	0.5hr	6hr	24hr	48hr	72hr
HYPO	IZ	0%	30%	30%	30%	36%	40%
	BZ	0%	7%	18%	10%	12%	22%
DYS	IZ	0%	45%	52%	40%	42%	49%
	BZ	0%	5%	10%	7%	10%	5%

Conclusions: 1) Once established at 0.5 hrs there was no significant change ($p>0.05$) in the extent of HYPO or DYS in the Infarct Zone and the Border Zone; 2) therefore improvements in the extent of HYPO and DYS between 0.5 and 72 hours may prove useful in assessing interventions designed to salvage myocardium.

NATURAL VARIABILITY OF WALL MOTION ABNORMALITIES FOLLOWING EXPERIMENTAL MYOCARDIAL INFARCTION: IMPACT ON THE ASSESSMENT OF INFARCT REDUCTION INTERVENTIONS

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If quantitative computer-aided echocardiography is to be instrumental in assessing the functional benefits of infarct reduction interventions, it is first essential to establish the 'natural' variability of abnormal (A) wall motion (WM). The purpose of this study, therefore, was to define the 95% confidence limits (CONF) for AWM in a canine infarct (MI) model. Serial short-axis echocardiograms were obtained in 10 closed-chest dogs at 0.5,6,24,48 and 72 hours (hrs) post MI, at the level of the apex, low papillary (PAP),mid PAP, high PAP and mitral valve (MV). WM was assessed by examining the radial excursion of 36 evenly spaced endocardial targets, every 16.7 msec, from end-diastole to end-systole. We quantified the circumferential extent (CE) of AWM by 3 methods: the number of radii with <10% and <20% fractional radial change (FRC) and a method that correlates radial excursion with 'normal' ray motion (CORR). The 95% CONF were calculated from the one-tailed values for the t distribution for the 95th percentile: 95% CONF = 1.92 X SD of the mean of the absolute difference in the CE of AWM at 6,24,48,72 hrs compared with 0.5 hrs. Results were (modal values):

	apex	low PAP	mid PAP	high PAP	MV
FRC<10%	40.5	19.7	31.4	15.2	17.6
FRC<20%	10.6	12.1	12.9	9.2	11.9
CORR	9.2	10.9	11.4	11.9	12.2

In order to demonstrate a significant ($p<0.05$) improvement in WM following an intervention, the degree of improvement must exceed the 95% CONF for AWM; we conclude, therefore, that this will depend on 1) the plane analyzed and 2) the method used to analyze AWM.

EVOLUTION OF THE TEMPORAL AND SPATIAL EXTENT OF DYSKINESIS FOLLOWING EXPERIMENTAL MYOCARDIAL INFARCTION

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The effect of infarct maturation on the temporal and spatial extent of dyskinesis has not been described. We used cross-sectional echocardiography to study the myocardial contraction sequence within the ischemic zones of 17 dogs, 30 min to 6 wks following acute infarction. Left ventricular short axis images were digitized from end-diastole to end-systole and fractional radial change along 36 evenly spaced rays calculated. The circumferential extent of dyskinesis (EXTENT) was determined for each decile of the normalized contraction sequence and the decile in which the greatest EXTENT occured was noted. The decile in which the maximal degree of dyskinesis (MAXDD) occured was also noted for each ray. RESULTS: The greatest EXTENT occurred in the 4th decile between 30 min and 48 hrs following infarction. The greatest EXTENT occurred progressively earlier in the contraction sequence as the infarct matured, with the maximal EXTENT occurring in the 3rd decile at 1 & 3 wks post-infarction and in the 1st decile at 6 wks post-infarction ($p=.001$). Similarly MAXDD occurred most frequently in the 4th or 5th decile during the early post-infarctional period (30 min to 1 wk), but during the 2nd and 1st deciles respectively, at 3 and 6 wks following infarction ($p=.001$). End-systolic dyskinesis was present in 30-50% of rays up to 1 wk following infarction, but was no longer observed at 6 wks. CONCLUSION: The maximal circumferential extent and degree of dyskinesis occur progressively earlier in the systolic contraction sequence as the infarct matures. Failure to recognize these changes in the myocardial contraction pattern may result in an underestimation of the degree of myocardial involvement.

IS MYOCARDIAL FUNCTION AFFECTED WHEN BLOOD FLOW TO NORMAL MYOCARDIUM IS INCREASED TO LEVELS ABOVE NORMAL?

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There is controversy regarding the effect of increasing blood flow to the normal myocardium in the intact animal. Accordingly, we studied the effect of selectively increasing blood flow to the normal myocardium in 12 open chest anesthetized dogs. Selective cannulation of the left circumflex artery (LC) was achieved in 6 normal dogs (Group I) while left main coronary artery cannulation was achieved in 6 dogs with LC occlusion (Group II). The experiment was conducted in 2 stages: stage 1 - cannulated artery pressure (CAP) = AO pressure (AoP), stage 2 - CAP>AoP. Myocardial thickening (MT) in the LC bed in Group I dogs and in the left anterior descending artery bed in Group II dogs (beds with normal blood flow) was measured using 2D echo. Additionally, thermodilution CO was measured in Group I dogs. The results (means) are as follows:

	n	Δ CAP(mmHg)	Δ CO(%)	Δ HR	Δ MT(%)
Group I	(6)	+62*	+ 8*	-2 †	+18*
Group II	(6)	+56*	-	-	+17*

*p<.05, † NS

Conclusion: Selectively increasing flow to the normally perfused myocardium increases regional and consequently global function in both nonischemic and ischemic left ventricles. This phenomenon may be related to increased intramyocardial diastolic stretch caused by increased blood flow into the myocardium. These findings may have therapeutic implications.

INTRINSIC CONTRACTILITY OF THE PAPILLARY MUSCLE IN NORMAL AND ISCHEMIC LEFT VENTRICLE IN VIVO - EXPERIMENTAL ECHOCARDIOGRAPHIC STUDIES.
Natesa Pandian, M.D., Shan Shen Wang, M.D., John Funai, M.D. Tufts-New England Medical Center, Boston, Massachusetts.

Although numerous investigators have used isolated papillary muscle (PM) to study cardiac muscle physiology, there are no precise data on the contractile dynamics of the PM in a normal beating heart. In addition, despite the implication of ischemic PM dysfunction in the development of mitral regurgitation, the effect of ischemia on the intrinsic contractility of PM has not been quantified in vivo. To examine the PM dynamics in normal and ischemic myocardium, we employed two-dimensional echocardiography with a 5 MHz transducer in 8 dogs and obtained images of the posteromedial PM in its long-axis (LAX) and short-axis (SAX), during control and during posterior wall ischemia induced by occlusion of circumflex coronary artery. From end-diastolic and end-systolic echo images we measured PM area in LAX, PM area and thickness in SAX and wall thickness (WT) of the subjacent myocardial wall (SMW) and remote myocardial wall (RMW) in SAX. Results: ($\bar{x}$±SE; *p<.01):

	% Δ during systole	
	Control	Ischemia
PM area change in LAX	37±5	6±2 *
PM area change in SAX	24±2	-9±3 *
PM thickening in SAX	22±5	-4±2 *
SMW thickening	22±5	4±2 *
RMW thickening	18±4	22±2 NS

Conclusion: The magnitude of intrinsic in vivo PM contraction is similar to that of subjacent myocardium in a normal ventricle. Ischemia profoundly impairs the intrinsic in vivo contractility of PM in addition to the dysfunction created in the subjacent myocardium.

CAVITY AREA - FLOW VELOCITY RELATIONS IN ACUTE MYOCARDIAL INFARCTION. EXPERIMENTAL ECHOCARDIOGRAPHIC STUDIES.
Shan Shen Wang MD, John Funai MD, Natesa Pandian MD. Tufts-New England Medical Center, Boston, Massachusetts.

To assess the effects of acute myocardial infarction (AMI) on aortic flow velocity (AoFV) and its relation to LV cavity area dynamics, we studied 9 heart-rate controlled dogs in whom AMI was created by left anterior descending coronary occlusion and infarction verified by TTC staining. We imaged the LV with 2D echo (2DE) and obtained AoFV recordings by Doppler echo (DE) in control (C) and hourly for 6 hours after coronary occlusion. From 2DE we measured LV cavity size frame-by-frame. From AoFV recordings we measured peak velocity (Vmax), velocity integral (VI) and acceleration rate (AR). Also, by relating the instantaneous changes in LV cavity size and AoFV, we measured the LV cavity area change required to accomplish peak velocity (VmaxAΔ) and total systolic LV cavity area change (TSAΔ) and derived two indices: VmaxAΔ/TSAΔ and Vmax/VmaxAΔ. Results: ($\bar{x}$±SD) (*p<.05 vs C).

	C	1 hr	3 hr	6 hr
Vmax(m/s)	.97±.2	.71±.1*	.61±.1*	.66±.2*
VI(cm)	13±2	10±2 *	9.2±1 *	10±3 *
AR(m/s/s)	20±6	12±5 *	9.7±3 *	11±6 *
VmaxAΔ/TSAΔ	16±6	31±12*	44±11*	31±10*
Vmax/VmaxAΔ	1.0±.2	.58±.2*	.39±1 *	.48±.2*

Although the changes in AoFV profile were significant in the group as a whole, Vmax, VI and AR displayed moderate overlap with C measurements; on the other hand, VmaxAΔ/TSAΔ and VmaxAΔ exhibited no significant overlap with control values. From these observations we conclude that: 1) AMI induced LVdysfunction results in adverse changes in AoFV, 2) Indices derived by relating LV cavity size change to aortic blood flow reflect pump function better than conventional indices and 3) pump dysfunction remains abnormal in the first 6 hours of AMI.

CHARACTERIZATION OF ACOUSTIC PROPERTIES OF ACUTE INTRACARDIAC THROMBI USING ULTRASOUND.
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Echocardiographic differentiation among intracavitary thrombus, cavity noise, and myocardium may be difficult. As an initial step toward thrombus characterization, 11 dogs were studied using an in vivo intracardiac thrombus model: apical coronary arteries were ligated and injections of 5% Na rescinoleate and 1000 units of thrombin at the endocardium-blood interface created left ventricular mural thrombus. Ultrasonic images were obtained in two views with a digital acquisition system, and a statistical analysis of echo intensities was performed in regions of interest in the thrombus, surrounding cavity, and myocardium. Acoustic characterization parameters included mean gray level, standard deviation (SD) and skewness. RESULTS:

Short-Axis Data (End-Systole, $\bar{x}$±SD)

Parameter	Thrombus	Myocardium	Blood
Mean	140.7 ± 7.6*	114.0 ± 3.8	103.0 ± 3.8
SD	15.7 ± 4.2*	11.0 ± 1.5	8.1 ± 1.1
Skewness	-0.03 ± 0.19§	0.04 ± 0.34	0.38 ± 0.22

(*p<0.001 thrombus vs. myocardium or blood, §p<0.01 thrombus vs. blood). Thrombus could be distinguished from myocardium only in views where regions of interest could be placed at similar depths of field. However, regardless of region of interest placement, all parameters distinguished thrombus from blood. CONCLUSION: acute intracardiac thrombus can be distinguished from surrounding blood and myocardium using ultrasound tissue characterization. These techniques may be clinically applicable.

LEFT VENTRICULAR FLOW PATTERN IN MYOCARDIAL INFARCTION ASSESSED BY POWER-MODE TWO-DIMENSIONAL COLOR FLOW MAPPING
Kiyoshi Machii, M.D., Hironori Hirai, M.D., Shigeru Nishizawa, M.D., Hideo Matsuzaki, M.D., Makoto Suzuki, M.D., Tetsu Yamguchi, M.D., Kenji Kuwako, M.D., Toho University, Tokyo, Japan.

Capability of power-mode two-dimensional color flow mapping for detection of a slow flow was assessed in 30 cases with myocardial infarction and 10 normal controls. The apparatus we used is either proto-type or commericially available Toshiba SSH-65A, in which both the power-mode and the conventional velocity-mode displays can be obtained. In the power-mode display, the total power of the backscattered ultrasound with Doppler effect is imaged in red or blue color according to the flow diretions. A unicolor display is also obtained by baseline shift operation. In normal subjects and 10 cases with a mild myocardial infarction, the left ventricular diastolic inflow directed toward the apex turned sharply to the opposite direction toward the outflow. In 12 cases with dilated left ventricle due to a uniform akinesis or hypokinesis of the left ventricular wall, a circular movement of the diastolic flow in the left ventricle could be visualized, and the lowest velocity imaged in color was arround 10 cm/sec, which was about one half of that with the velocity-mode display. In 8 cases with asynergy localized in the apex, flow in the apex could not be imaged. Our method is useful for assessing a swirling flow in dilated left ventricles, and for confirming a small asynergy localized in the apex.

PULSED DOPPLER-DERIVED MITRAL INFLOW VELOCITY IN ACUTE MYOCARDIAL INFARCTION: AN EARLY PROGNOSTIC INDICATOR.

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In order to determine the value of Doppler-derived mitral inflow characteristics as an early indicator of LV diastolic dysfunction in first, acute myocardial infarction, 60 patients (pts) were studied on admission. Age ranged from 55 - 71 years. Early peak diastolic velocity to peak Atrial velocity ratio (E/A) was obtained from an apical 4 chamber view with the sample volume at mitral annular level. Measurements from 5 cardiac cycles were averaged. E/A was related to worst Killip class during hospital stay and mortality. E/A decreased with Killip class: class I: 1.26±0.43 (n=25), II: 0.72±0.32 (n=21), III: 0.48±0.06 (n=7), IV: 0.42±0.06 (n=7). All 7 class IV pts died. In contrast, their admission class had been I (3 pts) or II (4 pts). E/A of ≤0.55 separated the 7 shock pts best. Sensitivity 100% and specificity 79% (7 false positives). E/A was poorly related with peak creatine-kinase ($r = -0.65$).

Thus: 1. There is a significant trend towards a lower E/A with a higher Killip class;
2. Assessment of E/A by pulsed Doppler on admission in pts with acute myocardial infarction helps to identify those at risk of subsequent death from cardiogenic shock.

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Hall D, Georgia World Congress Center
Echocardiography/Doppler

VALUE OF PREOPERATIVE M-MODE ECHOCARDIOGRAPHIC INDICES IN PREDICTING OUTCOME AFTER AORTIC VALVE REPLACEMENT IN SYMPTOMATIC PATIENTS WITH AORTIC REGURGITATION. K. John Heilman, III, M.D.; K.E. Hammermeister, M.D., FACC; Cecil Burchfiel, Ph.D.; Heidi Krause-Steinrauf, B.S.; Michael Crawford, M.D., FACC; Gulshan Sethi, M.D.; Participants in the VA Cooperative Study on Valvular Heart Disease.

The prognostic and functional significance of preoperative echocardiographic measurements was examined in 53 patients with pure aortic regurgitation (AR) undergoing aortic valve replacement (AVR) and followed prospectively for a mean of 34.3±15.6 months in the VA Cooperative Study on Valvular Heart Disease. Thirteen patients died, 4 intraoperatively. Preoperative left ventricular end-systolic dimension (LVESD), end-diastolic dimension (LVEDD), percent fractional shortening (LVFS), and end-diastolic radius to posterior wall thickness ratio (R/Th) did not differ significantly between survivors and non-survivors. The effect of preoperative LVESD and LVFS on postoperative LVEDD and functional class (FC) was examined in 25 surviving patients who had technically satisfactory echocardiograms six or more months after AVR.

	LVESD<5.5 (n=14)	LVESD≥5.5 (n=11)	LVFS≥25% (n=12)	LVFS<25% (n=13)
Preop LVEDD	6.7±.6	7.5±.9	6.8±.4	7.3±1.1
Postop LVEDD	5.4±.6	6.1±1.3	5.4±.5	6.0±1.3
Preop FC	2.4±1.0	2.7±.5	2.6±1.0	2.7±.7
Postop FC	1.5±.7	1.4±.6	1.5±.5	1.7±.6

LVEDD and FC improved significantly in all four subgroups postoperatively. Four year survival was similar in subgroups defined by preoperative LVESD or LVFS. We conclude that commonly used preoperative echocardiographic indices were not significantly predictive of survival, FC, or heart size postoperatively. Most patients can expect significant improvement in symptoms and decrease in LVEDD following AVR irrespective of preoperative LVESD or LVFS.

ABNORMAL RESPONSE TO THE VALSALVA MANEUVER IN PREECLAMPTIC PATIENTS DURING THE THIRD TRIMESTER OF PREGNANCY: EVIDENCE FOR ALTERED BARORECEPTOR FUNCTION. Louis J. Dell'Italia, MD, FACC, Raymond A. Dombroski, MD, Brent E. Finley, MD, Jackie Miller, Judy Vittitoe, RN, Michael H. Crawford, MD, FACC, and Robert A. O'Rourke, MD, FACC. Univ of Tx Health Sci Ctr, San Antonio, Tx.

The hemodynamic response to the Valsalva maneuver (VM) has been reported to be normal during the third trimester of pregnancy (preg). However, in patients (pts) with preeclampsia (PEC) we noted that during a sustained VM for >12 secs at 40mmHg: the systolic blood pressure (SBP) and heart rate (HR) remained unchanged during phase (PH) II, while there was an absence of reflex bradycardia during PH IV. We postulated that the increased (↑) blood volume of preg. preserved venous return and caused these abnormal hemodynamic results. Accordingly, we studied 10 third trimester pts with PEC with simultaneous ECG, SBP (cuff sphygmomanometer), and 2-D echo (apical 2 and 4 chamber views). LV volumes (V) were calculated with a microsonic digitizer using an area length formula for each view during 2 VM's. RV end-diastolic area (EDA) was obtained from the 4 chamber view. SBP did not decrease (↓) below control during PH II of VM. HR during PH II of VM did not ↑ significantly (85±7 [SD] to 85±20) and a reflex bradycardia was absent in 9 pts. RVEDA ↑ from 14.6±3.6 to 11.9±3.5cm^2 ($p<0.01$). Apical 2 chamber (76±14 to 62±16ml, $p<0.02$) and 4 chamber LVEDV's (72±16 to 53±18ml, $p<0.01$) ↓ significantly during PH II, as did LV stroke volumes (SV) (43±7 to 35±9ml, $p<0.05$; and 40±7 to 28±10ml, $p<0.005$, respectively). We conclude that in pts with PEC, SBP is maintained during PH II of VM despite a normal ↓ in RVEDA, LVEDV and LVSV. Since HR is unchanged, SBP is likely maintained due to altered baroreceptor function.

DIGITAL ECHOCARDIOGRAPHIC ANALYSIS OF LEFT VENTRICULAR FUNCTION AND ITS RESPONSE TO PHOSPHODIESTERASE INHIBITORS IN SEVERE CONGESTIVE HEART FAILURE

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To evaluate systolic and diastolic function in patients with NYHA class III-IV heart failure M-mode echocardiograms of the LV were recorded and digitized in 46 patients and compared to 40 normals. Peak diastolic filling rate (pDFR), peak and mean systolic ejection rate (pSER, mSER), peak posterior wall thickening rate (PWTK) and peak posterior wall thinning rate (PWTH) were measured. Results expressed in cm/sec, * = $p < 0.005$:

	pDFR	pSER	mSER	PWTK	PWTH
Normals	16.8±4.6	10.5±2.1	4.5±1.0	4.8±1.3	11.4±4.0
Patients	10.6±3.8*	6.2±2.2*	2.5±1.2*	3.9±1.7*	6.7±1.4*

The phosphodiesterase inhibitors enoximone or milrinone were given to a 10 patient subgroup in which simultaneous hemodynamic measurements and LV echocardiograms were performed pre and post acute drug administration. A borderline decrease in PA wedge pressure (18±7 to 16±7 mm Hg $p = 0.07$) and a significant increase in CI (2.0±0.4 to 2.3±0.4 L/min/m^2 $p < 0.001$) was noted. Corresponding digital echocardiographic results in cm/sec * = $p < 0.05$:

	pDFR	pSER	mSER	PWTK	PWTH
PRE	11.9±4.1	7.0±2.3	3.0±1.1	3.6±0.8	6.9±1.8
POST	13.4±5.2	8.4±3.4*	3.6±1.6*	4.9±1.8*	7.2±3.3

Conclusions: Both systolic (pSER, mSER, PWTK) and diastolic (pDFR, PWTH) indexes of LV function are significantly reduced to a relatively equal degree in severe heart failure. The hemodynamic improvement produced by phosphodiesterase inhibitors appears to result from improvement in indexes of systolic but not diastolic LV function.

CROSS-SECTIONAL ECHOCARDIOGRAPHIC DIMENSIONS IN CHILDREN: THE RELIABILITY OF NORMAL VALUES FROM SUBCOSTAL IMAGES

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The subcostal window is frequently used for the cross-sectional echocardiographic determination of cardiac chamber size in children. However, proper alignment of the long axis image of the heart from the subcostal window is more difficult than alignment of the 'equivalent' apical four chamber image. We hypothesized that this difficulty would increase the spread of the normal values determined for subcostal dimension (DIM) measurements. To test this hypothesis we 1) measured the supero-inferior (SI), medio-lateral (ML) and area DIM of the left atrium and left ventricle from the subcostal and apical four chamber images of 196 normal subjects, age 6 days to 18 years with BSA .18 to 2.1-m^2; 2) determined for each DIM, as an index of dispersion, the standard deviation (SDR) of the regression model: DIM = SLOPE * BSA + Y-INT; 3) compared the subcostal and apical four chamber SDR for each DIM.

RESULTS:

	APICAL		SUBCOSTAL		
DIM	N	SDR	N	SDR	SL
LA SI	148	.36	115	.61	p<.01
LA ML	146	.40	120	.47	p<.05
LA AREA	146	1.74	115	2.11	p<.05
LV SI	139	.52	108	.69	p<.01
LV ML	137	.46	109	.49	NS
LV AREA	136	2.78	109	3.63	p<.01

CONCLUSION: The significantly greater SDR of most subcostal left heart DIM indicates that the spread of subcostal DIM normal values is wider than for apical four chamber DIM. In children, therefore, DIM derived from the subcostal image may be less reliable for identifying quantitative abnormality.

PREOPERATIVE ASSESSMENT OF SURVIVAL AFTER VENTRICULAR SEPTAL RUPTURE.

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In order to determine preoperatively the survival after ventricular septal rupture, 31 patients with this infarct complication were studied by two dimensional echocardiography. By ECG 17 patients had posterior (post.) and 14 anterior (ant.) infarct. Each of 8 RV and 13 LV segments was graded on a 6 point scale from -1 (hyperkinesis) to +4 (aneurysmal). Wall motion score (WMS) of RV and LV was the sum of the scores for each segment. All patients had segmental asynergy of both RV and LV.

Results:	Ant.Infarct		Post.Infarct	
	LV-WMS	RV-WMS	LV-WMS	RV-WMS
survivors (n=13)	6.2±1.0 *	2.7±2.5 n.s.	3.6±2.5 n.s.	6.1±1.6 *
deaths (n=18)	15.1±2.6	2.6±1.9	1.9±3.3	12.2±2.8

* - p<0.01

Survivors with post.infarct had a RV-WMS of ≤8 and non-survivors ≥9. In ant.infarct survivors had a LV-WMS of ≤7, and non-survivors ≥12.

Thus, 1) Survival of ventricular septal rupture in ant. infarct appears to be determined by LV dysfunction, and in post.infarct by RV dysfunction.
2) Two dimensional echocardiography can be of help to identify preoperatively patients who may benefit from surgical intervention.

INCREASED EMBOLIC RISK IN PATIENTS WITH LEFT VENTRICULAR THROMBI.

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To determine the risk of systemic embolization from left ventricular thrombi, we followed 83 patients with echo-defined left ventricular thrombi (LVT) and compared them to a matched control group (n=86). The LVT and control groups were comparable with respect to recent (< 1 month) myocardial infarction (MI) (16% vs 21%), remote MI (74% vs 70%), anterior MI (80% vs 67%), cardiomyopathy (10% vs 9%), ejection fraction (30% vs 32%), echo referral for source of embolus (21% vs 22%), and followup duration (21 vs 22 months). Echoes were blindly read. The prevalence of definite central nervous system or peripheral emboli before echo and during followup was:

	Emboli Pre-Echo	Emboli in Followup
LVT (n=83)	18% (15/83)*	12% (10/83)*
Controls (n=86)	6% (5/86)	2% (2/86)

* p < 0.02 LVT patients vs. controls

Overall, 29% of LVT patients had emboli either pre-echo or during followup vs. 7% of controls (p < 0.001). In LVT patients, emboli during followup occurred a mean of 8.5 months (0.1-51) after echo and 30.7 months (2-72) after MI; 8 of 10 were in patients not on anticoagulants. In controls, 4 of 7 emboli were in patients with atrial fibrillation or flutter. The actuarial probability of being embolus free at 2 years was 86% in LVT patients vs 97% in controls (p < 0.02).

We conclude that left ventricular thrombi are associated with a definite increased embolic risk. The increased risk is not restricted to the immediate post-MI period, but continues indefinitely. Whether the long-term embolic risk would be reduced by chronic anticoagulant therapy at an acceptably low bleeding rate remains to be determined.

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ESTIMATION OF SHUNT VOLUME IN PATIENTS WITH OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT BY SUBCOSTAL 2D-ECHOCARDIOGRAPHY

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To determine whether shunt volume in patients (pts) with ostium secundum type atrial septal defect (ASD II) can be predicted by 2D-echocardiography (2D-echo) we studied 75 pts (mean age 37 ± 6 years) with ASD II who underwent right heart catheterization. The left-to-right shunt varied between 19 and 92 % (mean 51 ± 14 %); in 50 pts shunt volume was > 40 %. The endsystolic diameter of the atrial septal defect (ASD-ES) was visualized in 71 of 75 pts by subcostal 2D-echo. Additionally the relation of the enddiastolic right ventricular to left ventricular diameter (RV_{ED}/LV_{ED}) was determined from the apical fourchamber view. Because of the only fair correlation between ASD-ES and shunt volume (r = 0.74) and between RV_{ED}/LV_{ED} and shunt volume (r = 0.84), respectively, it was not possible to accurately predict the shunt volume. However, with an ASD-ES >20 mm in combination with a RV_{ED}/LV_{ED} - ratio > 1,2 it was possible to differentiate between hemodynamically insignificant shunts and shunts >40 %. The diagnostic value of both echocardiographic parameters to predict a shunt volume > 40 % was as follows:

Shunt volume > 40 %	Sensitivity	Specificity	Predictive accuracy
ASD-ES > 20 mm	92 %	95 %	93 %
RV_{ED}/LV_{ED} > 1.2	74 %	95 %	80 %
ASD-ED > 20 mm + RV_{ED}/LV_{ED} > 1.2	69 %	100 %	77 %

These data indicate that an ASD-ES > 20 mm in combination with a RV_{ED}/LV_{ED} - ratio > 1.2 is highly specific for a left-to-right shunt > 40 %; in this subgroup of pts with ASD II 2D-echo is able to replace right heart catheterization.

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SYSTOLIC ANTERIOR MOTION OF THE MITRAL VALVE IS TEMPORALLY RELATED TO PEAK PRESSURE GRADIENT IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

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The role of systolic anterior motion (SAM) of the mitral valve (MV) in the development of the pressure gradient in hypertrophic obstructive cardiomyopathy (HOCM) remains controversial. Seventeen patients with HOCM, 8 male, 9 female, aged 19-88 (mean 45 years) were studied with continuous wave Doppler echocardiography and were compared to 17 normal subjects. SAM and early closure of the aortic valve were present in 16/17 patients with HOCM, and were absent in the normal subjects. The time to peak outflow velocity as a percent of total systolic ejection time was 63% in HOCM versus 29% in normals ($p<0.001$). In 13/17 patients with HOCM, the time from R wave to closest approximation of the mitral valve to the septum during SAM was determined and was 242±66msec; the time from the R wave to peak velocity in these patients was 242±73msec, $r=0.90$. In 3 pts there was prolonged MV contact with the septum and the velocity peaked early and had a single spike. In the 10 pts with little or no contact of the MV with the septum, the Doppler waveform had a notched appearance and the peak velocity occurred when the MV was closest to the septum. There was no correlation between the time to peak velocity and the peak pressure gradient of the aortic outflow. Therefore, 1) peak outflow tract velocities occur significantly later in HOCM than in normal individuals and 2) the demonstration of the temporal relationship between SAM and peak outflow velocity in HOCM strongly suggests the importance of SAM in the development of dynamic outflow tract obstruction.

TRANSESOPHAGEAL TWO DIMENSIONAL ECHOCARDIOGRAPHIC EVALUATION OF BIVENTRICULAR DYNAMICS DURING POSITIVE END-EXPIRATORY PRESSURE VENTILATION.

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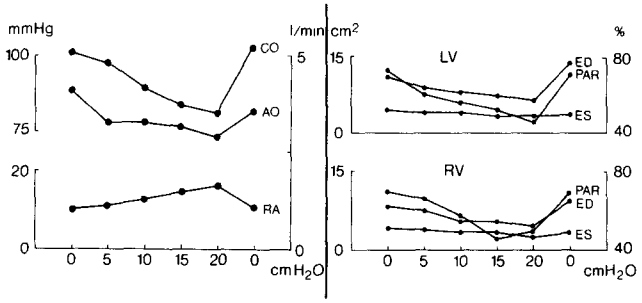
Since CO decrease during positive end-expiratory pressure is not fully understood RV and LV dynamics were studied by transesophageal two dimensional echocardiography in 21 stable patients shortly after coronary bypass surgery. All had normal RV and LV function before and after surgery. End-diastolic (ED) and end-systolic (ES) area, and percentage area reduction (PAR) of a RV and LV short-axis view were obtained during 5 cm H2O stepwise increments up to 20 cm. Simultaneously, mean AO and RA pressure, and CO were recorded.



Thus, CO decrease by positive end-expiratory pressure is caused by preload reduction rather than by impaired biventricular contractility.

LEFT VENTRICULAR MUSCLE VOLUME BY DIGITAL SUBTRACTION ANGIOCARDIOGRAPHY AND 2D-ECHOCARDIOGRAPHY

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Digital image processing can visualize myocardial dye perfusion in routine left heart angiocardiography using EKG and respiration gated background subtraction. Combination of myocardial and left ventricular image depicts the myocardial wall. The accuracy of derived mass and volume measurements was shown in previous experimental work. Imaging of left ventricular muscle wall is also achieved by 2D-echocardiography. In this study both methods were compared in respect of myocardial volume determination.
In 16 patients (3-78 kg, 5 days - 17 years) muscle volume was calculated from biplanar digital subtraction "myocardiograms" (multiple slices algorithm) obtained from standard levocardiograms (0.6-1.0 ml contrast/kg) and calculated from echocardiographic long and short axis views (sphere/ellipsoid model) both on the basis of manually outlined epi- and endocardial contours.
Comparison of both methods showed a good correlation for end diastole ($r=0.951$ SEE=27ml) and end systole ($r=0.924$ SEE=28 ml). Comparison between end diastole and end systole for each method revealed a close correlation of $r=0.994$ (SEE=9 ml) for digital myocardial imaging and $r=0.970$ (SEE=17 ml) for 2D-echocardiography.
2D-echocardiography renders reliable volume determination of left ventricular muscle wall irrespective of heart-phase.

ANEURYSMS AND DISSECTIONS OF THE DESCENDING THORACIC AORTA - IDENTIFICATION BY TRANSESOPHAGEAL TWO DIMENSIONAL ECHOCARDIOGRAPHY

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Aneurysms of the ascending aorta are easily detected by two dimensional echocardiography (2-DE) using the transthoracic approach (TTH 2-DE). However, TTH 2-DE may fail to yield diagnostic information about the descending thoracic aorta. To evaluate the usefulness of transesophageal 2-DE (TEE) in the detection of aneurysms and dissections of the descending thoracic aorta TTH 2-DE and TEE were performed on 14 pts (12 males, 2 females, mean age 54.4±18.1 years) with nondissecting aneurysms of the descending aorta (n=5) and with aortic dissections (DeBakey type I: n=4, type III: n=5).
Echocardiography was performed using a phased array sector scanner with a 2.25 MHz transducer for TTH 2-DE and with a 3.5 MHz miniature transducer at the tip of a 9 mm gastroscope for TEE.
In 4 pts with nondissecting aneurysms of the descending aorta the diagnosis could be established by TTH 2-DE, but in 1 pt the aneurysm was revealed only by TEE. In 2 pts with type I dissection the intimal flaps were identified and localized by TTH 2-DE, whereas 2 cases with type I dissection and all type III dissections could only be detected by TEE. Diagnosis was confirmed by angiography or surgery in all pts. No complication was observed using the transesophageal approach.
Thus, TEE is useful in the detection of aneurysms and dissections of the descending thoracic aorta.

TWO DIMENSIONAL ECHOCARDIOGRAPHY OF THE NON-INFARCTED MYOCARDIUM; PROGNOSTIC IMPLICATIONS OF REGIONAL HYPERKINESIS AND REMOTE ASYNERGY

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In order to determine the clinical significance of regional hyperkinesis (RH) and remote asynergy (RMA) of the non-infarcted myocardium, 98 patients were studied with a first, acute myocardial infarct. All patients were studied by two dimensional echocardiography within 12 hours after admission, and these findings were correlated with mortality and coronary angiography performed 3 weeks later. RH was present in 43/63 (68%) anterior and in 23/35 (66%) posterior infarcts; RMA in 11/63 (17%) anterior and 6/35 (17%) posterior infarcts.

	RH + (n = 66)	RH - (n = 32)	RMA (n = 17)
3-VD	6 (9 %) *	18 (56 %)	12 (71%)
2-VD	21 (32 %)	8 (25 %)	5 (29%)
1-VD	39 (59 %) *	6 (19 %)	0
Mortality	5 (7.5%) *	15 (47 %)	9 (53%)

* $p < 0.001$; VD = vessel disease

All 20 non-survivors (all anterior infarct) died within 30 days. In 15 of these (75%) RH was absent, and RMA was present in 9 (45%). RH was present in 5 non-survivors of whom 3 had a septal rupture.

We conclude: 1) Regional hyperkinesis is frequently found in both anterior and posterior infarcts. 2) Regional hyperkinesis is usually present in 1-VD and absent in 3-VD. 3) In patients with anterior infarct absence of regional hyperkinesis and/or presence of remote asynergy is associated with 3-VD and a high early mortality.

Tuesday, March 11, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 4:00PM–5:00PM
Hall D, Georgia World Congress Center
Cardiac Surgery

ILOPROST (ZK36374) PERMITS OPEN CARDIAC SURGERY DESPITE HEPARIN-INDUCED THROMBOCYTOPENIA.

Jeffrey R. Kappa, M.D.; Norig Ellison, M.D.; Carol A. Fisher, B.A.; and V. Paul Addonizio, M.D., University of Pennsylvania, Philadelphia, PA.

Heparin-induced thrombocytopenia (HIT) is associated with hemorrhage, idiopathic thrombosis, and sudden death. For 3 patients with confirmed HIT who required urgent cardiac surgery, we utilized temporary inhibition of platelet function with Iloprost (ZK), a new prostacyclin analogue, to prevent heparin-dependent platelet activation. In vitro, ZK prevented both heparin-induced platelet aggregation (82.1% without ZK; 3.3% with ZK) and ^{3}H Serotonin release (38.7% without ZK; 2.3% with ZK). A continuous infusion of ZK was begun 1 hr. prior to heparinization, was continued throughout cardiopulmonary bypass, and was discontinued 15 min after protamine administration. The mean platelet count of 130,000/ul remained stable and no spontaneous platelet aggregation was observed following heparinization. Plasma levels of platelet factor 4 rose from 26.3 to 843 ng/ml with heparinization and declined throughout bypass to 52 ng/ml indicating minimal platelet release. The mean bleeding time was 10.5 min preoperatively and 13.3 min postoperatively. The mean postoperative chest tube drainage(12 hrs) was 432 ± 67 ml compared to 515 ± 86 ml for 21 historical controls undergoing elective coronary artery bypass. Thus, despite confirmed heparin-dependent platelet activating factor in the plasma of these 3 patients, Iloprost prevented heparin-induced platelet activation during cardiopulmonary bypass and provided normal platelet function postoperatively as would be desired for hemostasis.

RECOVERY OF PLATELET FUNCTION AFTER CARDIOPULMONARY BYPASS - FRESH WHOLE BLOOD IS SUPERIOR TO PLATELET TRANSFUSION.

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Delayed recovery of platelet (PLT) count and function is the most common cause of bleeding after cardiopulmonary bypass (CPB). Recovery of PLT function was compared in 37 patients (pts) who were randomized to receive either one unit of fresh whole blood (FWB: 15 pts) or 10 PLT units (12 pts). PLT count, bleeding time, PLT aggregation (agg) (ADP, collagen, epinephrine) and thromboxane formation were abnormal after CPB in both groups. The increase in PLT count after FWB ($34\pm17 \times 10^{9}$ /l) was identical to that achieved by 4 units of PLT (31.5±15.4). The increase was higher after 10 PLT (69.3±32.7). The correction of bleeding time after CWB was identical to the effect of 8 PLT. However, thromboxane formation and recovery of PLT agg were better after FWB compared to 10 PLT units. (See Table).

	Agg (% recovery) Collagen	Epinephrine	Thromboxane (ng/ml)
FWB	84 ± 35	78 ± 29	95 ± 25
10 PLT units	55 ± 27	64 ± 24	46 ± 31
p value	<0.05	<0.05	<0.05

These results support the clinical observations of cardiac surgeons claiming the superiority of FWB in hemostasis after CPB.

PREOPERATIVE DIPYRIDAMOLE REDUCES POSTOPERATIVE BLEEDING

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Although antiplatelet agents may be contraindicated before cardiac surgery, dipyridamole (DIP) stabilizes platelet membranes and may reduce postoperative bleeding. A prospective randomized trial was conducted in 39 patients (pts) undergoing elective coronary bypass surgery. DIP was infused (0.24 mg/Kg/hr) preoperatively (22 hr before surgery), intraoperatively and for 36 hours postoperatively in 20 patients, and the patients in the control group (19 pts) did not receive DIP.

Dipyridamole preserved platelets (plat), leukocytes (WBC) and erythrocytes (RBC) on cardiopulmonary bypass and postoperatively. Arterial thromboxane B2 (TxB2 per platelet) levels were lower and 6-keto PG F1α (6-keto) levels were higher.

	Platelets $(x10^{9}$ /L)	WBC $(x10^{9}$ /L)	RBC $(x10^{12}$ /L)	TxB2/plat (pmolx10^{-6})	6-keto (µmol/L)
Hours	24	24	48	24	on bypass
DIP	156± 9*	9.6±0.9*	3.8±0.1*	7.2±1.4*	0.28±.04
No DIP	104±10	8.1±0.5	3.4±0.1	13.4±2.1	0.21±.05

Mean±SD * DIP different then no DIP $p<0.05$

Postoperative blood loss was reduced by 42% (DIP: 0.90±0.38*; No DIP: 1.5±1.2 L/pt @ 48 hr) and blood transfusion was reduced by 44% (DIP: 1.8±1.4*; No DIP: 3.3±2.4 units/pt).

CONCLUSIONS: Dipyridamole preserved platelets, leukocytes and erythrocytes, reduced platelet thromboxane production and enhanced endothelial prostacyclin release. Preoperative dipyridamole reduced postoperative blood loss and blood product utilization.

FAILURE OF THE MEMBRANE OXYGENATOR TO PREVENT COMPLEMENT ACTIVATION AND BLEEDING TIME PROLONGATION DURING CARDIAC SURGERY.

Kenneth G. Warner, M.D., Shukri F. Khuri, M.D., Francis D. Moore, Jr., M.D., Samar N. Assousa, B.S., Miguel Josa, M.D., C. Robert Valeri, M.D., West Roxbury VAMC, Brigham and Women's Hospital, Naval Blood Research Lab, Harvard and Boston University Medical School, Boston, Massachusetts.

Activation of the complement system (CS) and bleeding diathesis are important hematologic disorders associated with extracorporeal circulation (ECC). To compare the effects of two types of blood gas interfaces upon bleeding time (BT) and CS, 100 adult patients (PTS) undergoing cardiac surgery were randomized to either a bubble oxygenator (B, 50 PTS) or a hollow fiber membrane oxygenator (M, 50 PTS). Plasma levels of the complement cleavage product C_3a were measured in ng/ml using radio-immune assay and shown below:

	B		M		P
At cannulation	212 ± 38	*	251 ± 56	*	NS
20 Min of ECC	595 ± 78		600 ± 46		NS
120 Min of ECC	1246 ± 177	*	1041 ± 135	*	NS

*p<.0005

BT were similar at 2 hrs. postop (B:13.6 ± .7 mins and M:13.9 ± .7 mins, P:NS). Mean platelet count for all patients at 2 and 24 hrs post-op were 124 ± 6K and 118 ± 7K respectively with no difference between B and M. Likewise, there were no differences in blood loss, intraoperative or postoperative thromboxane B_2 and beta thrombo-globulin between the two groups. We conclude that the membrane oxygenator has no advantage over the bubble oxygenator in its effect on platelet function or on activation of the complement system during extracorporeal circulation.

DETERMINANTS OF INTRAMYOCARDIAL ACIDOSIS DURING CARDIAC SURGERY IN MAN.

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The spectrum and determinants of intramyocardial acidosis during cardiopulmonary bypass in man are unknown. Intramyocardial pH and temperature were continuously measured in 141 patients undergoing cardiac surgery. Temperature-corrected myocardial pH during the period of aortic cross-clamping (AC) ranged from 7.73 to 5.94. The mean integrated pH during this period (MpH) varied from 7.54 to 6.13 with an average of 6.85 ± .02. The patients were divided into two groups according to whether the MpH was above 6.87 (Group I, n=71, none to mild acidosis) or below 6.87 (Group II, n=70, moderate to severe acidosis).

	Group I	Group II	P
Valvular Heart Disease	17%	73%	.0001
LV Mass (gms)	244 ± 16	371 ± 27	.0001
Ejection Fraction (%)	59 ± 1.6	55 ± 1.8	NS
LVEDP (mmHg)	15 ± 0.9	20 ± 1.0	.001
pH Prior to AC	7.08 ± .02	6.83 ± .03	.0001
Period of AC (Min.)	55 ± 3.0	89 ± 4.1	.0001

Temperature variations were not significantly different in both groups. These data indicate that despite current myocardial protection techniques, intramyocardial acidosis is frequently encountered during cardiac surgery, and is determined primarily by the amount of LV hypertrophy, the magnitude of tissue ischemia at baseline, and the length of the cross-clamp period. Preoperative LVEDP and not ejection fraction also prognosticated the degree of intraoperative acidosis.

VALUE OF COLOR DOPPLER ASSESSMENT OF PULMONARY ARTERY PRESSURE IN CARDIAC TRANSPLANT PATIENTS.

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Tricuspid regurgitation (TR) was detected by color Doppler 53 times in 42 transplant patients (ages 16 to 65, mean 42 years). All studies were performed within 48 hours of right heart catheterization/biopsy. Pulmonary artery systolic pressure (PAP) was calculated from the Bernoulli equation ($4 \times TR\ peak\ velocity^2 + 10$ = PAP mmHg) by directing the continuous wave Doppler beam through the area of maximum turbulent flow detected by color Doppler. Color Doppler guided continuous wave PAP (range 20 - 74 mmHg) and those obtained by catheterization (21 - 74 mmHg) correlated well (r=0.85). In 5/7 transplant patients with biopsy proven rejection (in myocyte necrosis) PAP was higher (34 - 40 mmHG) during the rejection episodes as compared with absence of rejection (17 - 22 mmHg) and these increases in PAP were reliably identified by color Doppler in all. In the remaining two patients rejection was identified by the new development of TR which disappeared after therapy/absence of rejection. In 8 pre-transplant patients, color Doppler reliably predicted PAP (36 - 74 mmHg, r=0.96). Two patients with high PAP (both 74mmHg) underwent heterotopic transplant while 6 with lower PAP (36 - 60mm Hg) had orthotopic transplant. In conclusion, color Doppler predicts PAP reliably and noninvasively in pre and post transplant patients. This has potential value in identification of rejection and in selecting the type of transplant.

CAN DOPPLER ECHOCARDIOGRAPHY REPLACE CARDIAC CATHETERISATION IN THE POSTOPERATIVE HAEMODYNAMIC ASSESSMENT OF THE ARTERIAL SWITCH PROCEDURE?

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Nineteen children who had undergone the arterial switch operation for transposition of the great arteries between the ages of 1 week and 10 years underwent pulsed and continuous wave Doppler examinations, 1 month - 98 months following surgery. Mild aortic regurgitation was detected in 10, but systolic aortic velocities were normal in all but 1. High flow velocities at pulmonary valve level, at the pulmonary artery bifurcation or in the left pulmonary artery were detected in 14 patients. Doppler sampling of the right pulmonary artery was not achieved. The site of obstruction to pulmonary flow and the presence and severity of aortic regurgitation detected by Doppler correlated well with cardiac catheterisation performed in 16 patients at a mean interval of 35 months prior to this study. Peak velocities across the mitral and tricuspid valves were significantly higher than normal, suggesting that ventricular compliance in this group of patients may differ from normal. No pathological atrioventricular valve regurgitation was seen. Doppler echocardiography provides valuable information following the arterial switch operation and may avoid the need for repeat cardiac catheterisation. However, branch pulmonary artery stenosis may be difficult to detect with Doppler and occurred in 3 patients following the LeCompte manoeuvre.

PROSPECTIVE NON-INVASIVE ASSESSMENT OF BIOPROSTHETIC DYSFUNCTION: CATHETERIZATION IS NOT REQUIRED PRIOR TO SURGERY.

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From September 1984 to July 1985 11 patients (6 mitral and 5 aortic) were seen with suspected bioprosthetic dysfunction. All were examined by echo & doppler cardiography. Six patients had primary degeneration (PG) and four had infective endocarditis (IE), and 1 had a paravalvular leak. Of those with PG a torn cusp was seen in 3, calcium in 3, and evidence of aortic insufficiency in 1. Two of the IE patients had definite vegetations and 2 had valve thickening. Doppler cardiography detected an increased transvalvular gradient (16-30mmHg) in 4/5 with mitral dysfunction and an increased gradient (52-81mmHg) in 4/5 with aortic valve dysfunction. Aortic insufficiency was seen in 5/5 with aortic valves. Cardiac catheterization was performed in 3 patients with aortic valve dysfunction and confirmed the non-invasive observations. One patient with mitral valve dysfunction had a perivalvular leak found at catheterization which was not detected by doppler. Severe pulmonary hypertension was found by doppler in one patient with a calcified stenosed mitral valve. This was confirmed at surgery. All 11 have had their dysfunctional valves replaced with confirmation of the echo-doppler findings. We conclude that quantitative echo-doppler cardiography alone can be employed to diagnose prosthetic valve dysfunction in a large majority of patients, the data is sufficient for surgical intervention without resorting to cardiac catheterization.

USE OF THE 12-LEAD ECG IN PREDICTING VENTRICULAR TACHYCARDIA SITE OF ORIGIN: SURGICAL IMPLICATIONS

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ECG's (12-lead) of 166 distinct ventricular tachycardias (VT) in 106 patients with prior infarcts were related to endocardial sites of origin (using catheter or operative mapping) to determine if any ECG patterns were specific for site of origin. ECG's were analyzed according to bundle branch block (BBB) type, axis (quadrant), precordial R wave progression (RWP) and infarct location. There were 100 right-BBB VT and 66 left-BBB VT. ECG's in 43 (65%) left-BBB VT, but only 16 (16%) right-BBB VT, were specific for site of origin ($p<.001$). Specific patterns (occurring >5 times; positive predictive accuracy >65%) were:

ECG (BBB/axis/RWP)	Infarct	Origin	Accuracy
1)Left BBB/left superior no RWP	anterior	inferoapical septum	16/17 (94%)
2)Left BBB/left axis/ normal RWP	inferior	inferobasal septum	15/18 (83%)
3)Left BBB/inferior/ any RWP pattern	anterior	anteroapical septum	12/14 (86%)
4)Right BBB superior/ reverse RWP	inferior	inferobasal free wall	11/16 (69%)
5)Right BBB/right inferior/reverse RWP	inferior	inferobasal free wall	5/6 (86%)

All other ECG patterns had variable origins (58 VT), or occurred <5 times (37 VT). Thus: 1) Prediction of site of origin from ECG pattern is more accurate with left-BBB VT than right-BBB VT. 2) Regionalized surgical ablation can be performed based on VT-ECG criteria in 43% of VT, but 3) In VT having nonspecific ECG patterns (57% of VT), mapping is still needed for guided surgical ablation.

CONTRAST ECHOCARDIOGRAPHY: THE NEW GOLD STANDARD FOR INTRAOPERATIVE EVALUATION OF VALVULAR REGURGITATION.

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Because of superior hemodynamics and avoidance of long-term anticoagulation, valve repair is preferable to valve replacement. However, significant valvular regurgitation (VR) may persist following conservative valvular surgery, and if undetected, precludes a successful result. Present methods for the detection of VR intraoperatively (OR) by direct palpation (palp) and pressure tracings are inaccurate. We have successfully utilized 2-dimensional contrast echocardiography (2DCE) to detect VR OR. A sterilely prepared transducer placed directly on the heart continously images as 5 ml's of saline is injected through a needle into the left or right ventricle generating microbubbles (contrast) which normally exit antegrade. With VR, systolic reflux of contrast is seen in the respective atrium, and is graded on a scale of 0-4+, as in ventriculography (cath). 2DCE was compared to direct OR palpation in 28 patients: 16 with cath documented mitral regurgitation (+MR) 12 without (-MR).

	Cath	2DCE	Palp
+MR	16	16	11
-MR	12	12	17

Compared to cath the sensitivity and specificity for detection of MR was 100% and 100% by 2DCE and 69% and 100% by palpation. Importantly, besides failing to detect MR in 5 patients, palp could not quantify severity of VR. However, 2DCE could accurately detect both the presence and severity of OR VR. 2DCE may become the "gold standard" for OR evaluation of VR.

IMPROVED SURGICAL OUTCOME IN PATIENTS WITH VENTRICULAR TACHYCARDIA WITH REPEAT ENDOCARDIAL MAPPING AFTER INITIAL SUBENDOCARDIAL RESECTION DURING NORMOTHERMIC BYPASS.

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The standard surgical approach in patients (pts) with ischemic heart disease and sustained monomorphic ventricular tachycardia(VT) involves endocardial mapping followed by subendocardial resection(SER) during hypothermic cardioplegia. Failures of the technique are often due to either imprecise mapping or to the subsequent appearance of VT of different morphology. To circumvent those limitations we repeated endocardial mapping during normothermic partial bypass after an initial SER in 13 consecutive pts with VT that could be initiated and endocardially mapped at operation. The group included 11 males and 2 females with a mean age of 57±10 yrs(±SD) and left ventricular ejection fraction of 31±14%. After the first map-directed SER 9/13 pts(69%) had in response to programmed stimulation monomorphic VT with either a similar (3pts) or different(6pts) morphology. In these latter 9 pts, 2.8±1.4 (range 1-5) additional sequences of endocardial mapping followed by SER were repeated until monomorphic VT could no longer be initiated in any pt. Mean normothermic bypass time was 72±27 min with a total bypass time of 116±40 min. There were 2 operative deaths; both occurred in pts who were in shock before operation. Of 11 operative survivors, 10 had no VT induced at post-operative electrophysiologic study. These 10 pts and 1 pt on antiarrhythmic therapy remain free of clinical VT 12±8 months after surgery.

Thus, repeat programmed stimulation, endocardial mapping and SER after initial resection permits localization and sequential ablation of residual VT with disparate sites of origin. This technique is technically feasible, and improves electrophysiologic results of surgery.

VASODILATOR DRUGS AND LUMINAL SIZE OF BYPASS GRAFTS.
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It is still unclear whether vasomotor tone can be present in aortocoronary vein grafts (ACVB) late after operation, that may be mediated by vasodilator drugs. We studied the effects of nitroglycerin (NTG), nifedipine (NIF), and dipyridamole (DIP) on blood flow and luminal diameter (D) of 35 patent ACVB in 33 patients 6 to 20 months after surgery. From calibrated biplane cineangiograms D-ACVB was derived as the average of at least 10 equidistant diameter measurements in each plane. Graft flow (Q) was assessed by videodensitometry from tape-stored videoangiograms taken concomitantly with cineangiography. Measurements were performed before and 4 min after 0.8 mg NTG sublingually (sl), 8 min after 10 mg NIF sl, and 1 min after 0.2 mg NTG or 0.5 mg/kg DIP injected directly into the bypass (ib). Mean values ± SE were (*: p<0.05 vs control values before drug):

		NTG sl n = 12	NTG ib n = 6	NIF sl n = 8	DIP ib n = 9
D-ACVB (mm)	Control	3.5±0.8	3.5±0.8	3.4±0.5	4.0±0.8
	Drug	3.5±0.8	3.6±0.8	3.4±0.5	4.0±0.8
Q-ACVB (ml/min)	Control	57±15	42±14	50±11	49±10
	Drug	50±14*	49±16*	66±13*	86±24*

Differences in luminal bypass diameter before and after drug administration did not exceed ± 6 % in any patient.

Conclusions: Although these potent vasodilator drugs induced significant changes in bypass blood flow, they did not alter bypass lumen to any significant extent. Our data, therefore, do not give any evidence for the presence of vasomotor tone in venous bypass grafts at later stages after operation, but support the contention of a fixed conduit.

INFLUENCE OF CHOLESTEROL ON LATE GRAFT PATENCY IN 322 PATIENTS FOLLOWED UP TO 14 YEARS AFTER CORONARY BYPASS
Gerald M. Lawrie, M.D., FACC, George C. Morris,Jr., M.D. FACC, Steven Thomas, Donald Glaeser, D.Sc.
Baylor College of Medicine and The Methodist Hospital Houston, Texas

In order to determine the influence of total cholesterol (TC) on late coronary vein graft patency 322 patients (pts) from a series of 1447 pts followed 10-14 years, were analyzed. These 322 pts had undergone post-operative graft evaluation at a mean of 65.2 months (1-178 months). Multiple clinical angiographic and laboratory values were similar for these pts and the remaining 1125 pts. TC was 249.6+53.5mg% in unstudied vs 256+56.9mg% for studied pts. (p>0.12) Pts were classified angiographically as normal (189 pts) or abnormal (133 pts). Abnormal pts had 1 or more stenotic and/or occluded grafts. TC was 251+58.8mg% for normal pts and 264+53.8mg% abnormal pts (p>0.05) A 10 year Kaplan-Meier analysis was performed for 4 groups of pts: TC<200, ≥200<245, ≥245<280, >280 mg%. There was no difference in incidence of graft abnormalities among these 4 groups (p>0.05). Cox, two-way table and logistic regression analyses of multiple variables showed no association between TC and graft abnormality. Only the number of grafts performed was predictive of graft failure.

In conclusion, unlike coronary atherosclerosis, TC at the usual levels encountered in these pts does not significantly influence the occurrence of graft occlusion or stenosis over a 10-14 year period.

Tuesday, March 11, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 4:00PM–5:00PM
Hall D, Georgia World Congress Center
Cardiac Surgery

SHOULD AIRLINE PILOTS FLY FOLLOWING CORONARY BYPASS SURGERY?-A CASS REGISTRY STUDY
Bernard R. Chaitman, MD, FACC, Kathryn B. Davis, PhD, Harold T. Dodge, MD, FACC, Lloyd D. Fisher, PhD, FACC, George C. Kaiser, MD, FACC, and CASS hospitals. Saint Louis University School of Medicine, St. Louis, MO

The risk of sudden incapacitation after coronary bypass surgery is a major problem in formulating guidelines for recertification of individuals whose occupation carries an important risk to public safety. To address this issue, we selected a subset of CASS registry pts to simulate an airline pilot population and prospectively determined the 5 year incidence of acute cardiac events (acute coronary insufficiency, myocardial infarction, or sudden death) following coronary bypass surgery. Patients over 60 years, or those with diabetes, moderate-severe hypertension, congestive heart failure, perioperative myocardial infarction or significant noncardiac medical illness were excluded as were pts who became symptomatic in the year following operation. The annual incidence of acute cardiac events in the 1207 men who met these criteria was 1.6 + 0.2% (SEM). Cox regression analyses of 14 clinical and angiographic variables selected smoking and mild hypertension as the only significant predictors of acute cardiac events. The annual event rate in 838 normotensive patients who either never smoked, were former smokers, or were current smokers was 0.4 ± 0.3%, 1.0 ± 0.3%, and 2.2 ± 0.5%. The 5 year incidence in patients with mild hypertension who never, were former, or current smokers was 1.4 ± 0.7%, 1.8 ± 0.7%, and 2.8 ± 0.9% respectively. Thus, the incidence of acute cardiac events after coronary bypass surgery is small in subsets of a simulated airline pilot population. These data are pertinant to the question of pilot recertification post coronary bypass surgery.

DETERMINANTS OF DISCHARGE FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY
Harold Lazar MD, Kenneth Wilcox MD, Carolyn McCabe BS, John McCormick MD, FACC, and Arthur Roberts MD, FACC, Boston University Medical Center, Boston, MA

Earlier discharge (d/c) following coronary artery bypass grafting is mandatory in today's cost-containment climate. The optimal time for discharge following coronary artery bypass grafting (CABG) remains controversial and varies among institutions. This study was undertaken to identify what variables may discriminate between early and late discharge following CABG. In 177 consecutive patients undergoing isolated CABG, 3 groups were formed based on the number of days hospitalized post CABG: Group I ≤ 8, Group II 9-11, Group III ≥ 12. Variables which discriminated between early and late discharge were:

Variable	Group I (n=50)	Group II (n=79)	Group III (n=48)
Female Gender	5	14	20*+
Unstable Angina	4	18*	20*+
Heart Failure (CHF)	3	18*	13*
Age ≥ 65 years	5	22	33*+

*p < .05 from Group I +p < .05 from Group II

Variables which did not discriminate between early and late discharge included prior MI, hypertension, smoking, diabetes, crossclamp time, number of bypass grafts, EF < 40%, or PTCA failure. Group I patients had no increase in return visits or readmissions < 60 days post CABG. These data suggest that certain patients can be safely discharged ≤ 8 days after CABG. Female sex, age ≥ 65 years, unstable angina and CHF are variables which predispose to longer hospitalizations. These data should prove useful to surgeons in determining earlier discharge criteria following CABG surgery.

COMBINED VALVE PROCEDURE AND BYPASS SURGERY IN SEPTUAGENARIANS AND OCTOGENARIANS - RESULTS IN 120 PATIENTS.
Tsung-Po Tsai, M.D., Jack Matloff, M.D., Aurelio Chaux, M.D., Robert Kass, M.D., and Myles Lee, M.D. Cedars-Sinai Medical Center, Los Angeles, California.

Consecutive 96 septuagenarians (sept)(male 63, female 33, 74) and 24 octogenarians (oct)(male 9, female 15, 83) underwent combined valve procedure and bypass surgery with cardiopulmonary bypass using hypothermia (21°C) and hyperkalemic cardioplegia. Most patients (pts) were in NYHA Functional Class III (sept 35%, oct 12%) and Class IV (sept 57%, oct 88%) preoperatively. There were 19 early sept deaths (19.8%) and 9 early oct deaths (37.5%). Late mortalities were 7 sept (9%) and 1 oct (6.6%) in a 6 month (mo) to 4 year (yr) follow-up (25 mos). Of 84 over 30-day survivors, 78% of sept and 87% of oct pts improved by one or more NYHA classes postoperatively.

23% sept and 47% oct pts developed major complications that included bleeding, tamponade, sternal dehiscence, MI, arrhythmia and pump failure. Mortalities were adversely influenced by 1) NYHA Class IV (sept 38% vs oct 43%), 2) Postoperative hemorrhage (sept 16% vs oct 22%), and 3) Prolonged ischemic aortic cross-clamp time (over 100 minutes, sept 30% vs oct 50%).

Total mortalities in Aortic Valve Replacement (AVR) + Coronary Artery Bypass (CAB) Group, Mitral Valve Replacement (MVR) + CAB Group, Aortic and Mitral Valve Replacement (DVR) + CAB Group, and Mitral Valve (MV) Repair + CAB Group were: 21%, 50%, 22%, and 18% respectively. Comparing those groups with isolated valve replacement in the same period (44 mos), mortalities in the AVR, MVR and DVR Groups were 7%, 29% and 33%.

Conclusion: The risk of combined valve procedure and bypass surgery was significantly increased in the elderly and may warrant a less aggressive procedure, especially in the mitral position.

CRYOABLATION OF RIGHT VENTRICULAR TACHYCARDIA: IMPLICATIONS IN ISCHEMIC HEART DISEASE.
Jorge Cheirif, MD, Gerald M Lawrie, MD, FACC, Karen J Beckman, MD, Jack Krafchek, MD, Sharon A Magro, PAC, Christopher R C Wyndham, MD, FACC.
Baylor College of Medicine, Houston, TX.

Ventricular tachycardia (VT) with right ventricular (RV) endocardial breakthrough usually occurs in patients (pts) without ischemic heart disease (IHD). That VT with RV breakthrough can occur in IHD has not been previously emphasized. We encountered 14 out of 46 pts (34 with IHD) operated upon for VT, in whom earliest endocardial breakthrough was in the RV. Pts failed a mean of 3.8 antiarrhythmic drugs. Of the 14, 10 pts had IHD with prior infarction, 2 had tetralogy of Fallot, 1 arrhythmogenic RV dysplasia and 1 cardiomyopathy. Twenty-seven VTs were documented in the 14 pts; one VT in each pt (all QS or rS in lead V1) showed earliest activation in the RV: septum in 9, free wall in 4 and crista supraventricularis in 1 pt. Of 10 pts with IHD, earliest activation was in RV septum in 8, free wall in 1, crista in 1 pt. RV breakthrough occurred from -145 to +8 (mean -45 ± 38) msec relative to onset of QRS during VT. Surgery involved RV CR in 13 pts and RV septal endocardial excision in 1 pt. Concomitant procedures included left ventricular (LV) CR in 7, LV endocardial resection in 6, LV aneurysmectomy in 6, RV outflow repair in 2, VSD closure in 1 and RV disconnection in 1 pt, without complications. Postoperatively VT was initiated by programmed stimulation in the 1 pt with IHD who did not have RV CR; VT recurred in this pt and one other with IHD with a VT never seen before. We conclude that in approximately 30% of pts with VT and IHD, VT may arise in RV endocardium and require RV surgery. Cryoablation is an effective and safe therapy for drug-resistant tachycardia.

Tuesday, March 11, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 2:00PM–3:00PM
Hall D, Georgia World Congress Center
Electrocardiography/Ambulatory Monitoring

DYSRHYTHMIAS ON SHORT TERM HOLTER AS AN INDEPENDENT PREDICTOR OF MORTALITY IN CONGESTIVE HEART FAILURE.
Ross D. Fletcher, M.D., F.A.C.C.; Donald Archibald, Joseph Orndorff, R.N.; Jay Cohn, M.D., F.A.C.C. The Cooperative Study Group, VA Medical Center, Washington, D.C.

To determine if ventricular dysrhythmia is an independent risk factor or merely a marker for left ventricular dysfunction we examined outpatient short-term Holter (STH) at the time of randomization of 346 pts with CHF into a VA Cooperative Study designed to test efficacy of vasodilator therapy. Direct reading of tapes on dual channel compacted print-out averaged 4.5±1.2hrs. mean follow-up was 2.3yrs. When PVC average increased from <10 to >10/hr, annual mortality rate (AMR) increased from 11% to 20% p<.001). Modified Lown grade predicted increasing AMR; no PVC 6.3%; unifocal 10.8%; multifocal 13.3%; couplets 17.1%; triplets and runs 24.1% p<.001. While presence of coronary artery disease (CAD) or low ejection fraction (EF<median of 28%) increased AMR, runs on the STH independently doubled AMR in life table regression p<.001. Runs increased AMR in each subgroup as follows:

	No runs		Runs		
Etiology	N	AMR	N	AMR	P
No CAD	124	11%	63	23%	<.01
CAD	125	17%	34	37%	<.001
EF					
>28	112	9%	37	16%	<.001
<28	103	21%	33	32%	<.04

Thus, dysrhythmias on STH contribute independently to mortality in CHF of coronary and noncoronary etiology at all levels of left ventricular dysfunction.

PREDICTIVE ACCURACIES OF HOLTER MONITORING AND PROGRAMMED STIMULATION IN PATIENTS TAKING AMIODARONE.
Soo G. Kim, M.D., F.A.C.C., Samuel D. Felder, M.D., Ilona Figura, M.D., Lawrence E.Waspe, M.D., F.A.C.C., John D. Fisher, M.D., F.A.C.C., Montefiore Hospital, Bronx, N.Y.

Predictive accuracies of Holter Monitoring and programmed stimulation (PES) were evaluated in 50 patients (pts) on amiodarone (amio) for recurrent, sustained ventricular tachycardia (VT). Before amio, all had inducible VT by PES (1-3 extrastimuli) and frequent (≥30/hr) ventricular premature complexes (VPCs) on Holter. Amio therapy (865±271 mg/day for 16±9 days) was effective (negative) by PES (VT not inducible or ≤15 beats) in 9 pts and ineffective (positive) in 41. Amio was effective by Holter (≥85% reduction of VPCs and abolition of VT, defined as negative) in 42 and ineffective (positive) in 8. All pts were discharged on amio and followed for 20±19 months. Sixteen pts with follow-up less than 1 year, without recurrence, were excluded from 1-year survival analysis. One year after discharge, 25 pts had no recurrence (Holter negative in 23, positive in 2; PES negative in 6, positive in 19) and 9 had recurrence (Holter negative in 5, positive in 4; PES negative in 1, positive in 8). From 1-year survival data, predictive accuracies (PA) and positive (+) and negative (-) predictive values (PV) were obtained. (+)PV=positive Holter or PES with recurrence. PA=(true positive + true negative)/all pts.

	Sensitivity	Specificity	(+)PV	(-)PV	PA
PES	89%	24%	30%	86%	41%
Holter	44%	92%	67%	82%	79%

Conclusion: In pts with recurrent VT and frequent VPCs before amio, positive PES on amio is non-specific and positive Holter is insensitive. The negative PV of Holter and PES are similar but the positive PV of PES is poor. The PA of Holter appears to be superior to that of PES.

THE UTILITY OF EARLY HOLTER MONITORING IN PREDICTING CLINICAL EFFICACY OF AMIODARONE IN VENTRICULAR TACHYCARDIA.

Steven L. Ballas, M.D., Enrico P. Veltri, M.D., Lawrence S.C. Griffith, M.D., F.A.C.C., Thomas Guarnieri, M.D., F.A.C.C., Philip R. Reid, M.D., F.A.C.C. The Johns Hopkins and Sinai Hospitals, Baltimore, Maryland.

To determine the utility of Holter monitoring(HM) during the early phase of therapy with amiodarone in predicting subsequent clinical events, 96 patients(pts) with symptomatic ventricular tachycardia(VT) were evaluated. The population characteristics included: 79 males, 17 females; age 60±13 years (mean ± standard deviation); coronary artery disease in 71(74%), cardiomyopathy in 15(16%), valvular heart disease in 3(3%), congenital heart disease in 2(2%), primary electrical disease in 5(5%); ejection fraction 36±15%. Clinical presentations were sudden death in 38(40%), syncope in 31(32%), presyncope in 27(28%). All pts had baseline 24 hour HM off all antiarrhythmic drugs > 5 half-lives revealing nonsustained VT(≥3 beats). Amiodarone was administered 1200 mg/day for 14 days then 200-400 mg/day maintenance and HM was performed during the second week of therapy (days 8,9,10). There were 66 pts(69%) without VT on HM and 30 pts(31%) with VT noted on second week HM. At 17±12 months followup, 35 pts(36%) had clinical arrhythmic events (sudden death, sustained VT, syncope): 13 of 66(20%) without VT on HM and 22 of 30(73%) with VT on HM($p<.001$). The table below depicts the value of VT on early HM in predicting subsequent clinical efficacy:

Sensitivity	63%
Specificity	87%
Positive predictive value	73%
Negative predictive value	80%
Predictive accuracy	78%

We conclude that in pts with clinical symptomatic VT who manifest nonsustained VT on baseline HM, early HM on amiodarone therapy predicts long-term efficacy.

POOR PREDICTIVE VALUE OF PERSISTENT INDUCTION OF VENTRICULAR TACHYCARDIA BY PROGRAMMED STIMULATION DURING CONVENTIONAL ANTIARRHYTHMIC THERAPY EFFECTIVE BY HOLTER CRITERIA. Soo G. Kim, M.D., F.A.C.C., Sam Felder, M.D., Lawrence E. Waspe, M.D., F.A.C.C., John D. Fisher, M.D., F.A.C.C. Montefiore Medical Center, Bronx, N.Y.

While prevention of induction of ventricular tachcardia (VT) by programmed stimulation (PES) during a therapy is highly predictive of clinical efficacy, the value of persistent induction of VT by PES in predicting clinical inefficacy of a therapy has been questioned in patients (pts) taking certain agents (propafenone or amiodarone). The predictive value of persistent induction of VT during a therapy with conventional agents (procainamide, quinidine, disopyramide, propranolol and phenytoin) effective by Holter criteria was studied in 36 pts with recurrent sustained VT. All had frequent (> 30/hour) ventricular premature complexes (VPCs) and inducible VT by PES (1-3 extrastimuli) at baseline. A therapy was effective by PES criteria (VT no longer inducible or ≤ 15 beats) in 17 pts (group 1). Remaining 19 pts (group 2) were discharged on a therapy ineffective by PES but effective by Holter criteria (> 83% reduction of VPCs and abolition of VT). Duration of follow-up was 18.0 + 12.3 months. Five pts had recurrences within 12 months (2 in group 1, 3 in group 2: P=NS). Arrhythma-free survival rates by Kaplan-Meier's method at 6,12,18 and 24 months were 82%, 82%, 72% and 60% in group 1 and 89%, 77%, 70% and 70% in group 2 respectively (P=0.343 by Logrank test).

Conclusion: In selected pts with frequent VPCs at baseline, persistent induction of VT during a therapy with conventional agents has poor value in predicting clinical inefficacy and does not preclude good clinical outcome if the therapy is effective by Holter criteria.

IS 24 HOURS AMBULATORY ELECTROCARDIOGRAPHY USEFUL IN PREDICTING MORTALITY OF LOW RISK SURVIVORS OF MYOCARDIAL INFARCTION (MI)?

John B. Kostis, M.D., F.A.C.C., Robert P. Byington, Ph.D., Marvin L. Murphy, M.D., F.A.C.C., Lawrence M. Friedman, M.D. for the BHAT Study Group

Ventricular ectopic activity (VEA) is associated with increased mortality in survivors of MI but its relative prognostic importance in patient subsets with high or low risk has not been adequately explored. One thousand three hundred seventy four survivors of acute MI randomized to the BHAT placebo group were stratified according to the presence or absence of three easily obtainable clinical criteria (history of prior MI, cardiomegaly, ST depression on 12 lead resting ECG).

Presence of VEA (10 VPB/h or pairs or VT or multiform) was associated with increased risk in all strata over an average 25 month (12 to 40 months) follow-up.

#Clinical Criteria Present	N	% Mortality Overall	With VEA	Without VEA	Relative Risk	Z
None	591	4.7	9.1	2.4	3.86	3.68
any 1	547	11.5	15.8	8.7	1.81	2.53
any 2	205	19.0	21.1	16.5	1.28	0.83
all 3	31	35.5	41.2	28.6	1.44	0.73

Similar results were obtained when sudden (1 hour) death was considered.

Therefore:

1) Inexpensive easily available clinical criteria can be used to categorize risk of death in MI survivors over an 8-fold range.
2) VEA is associated with increased mortality in all risk categories.
3) Relative risk tends to be higher in the low risk strata.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #313/314
Doppler Echocardiographic Assessment of the Right Heart

COMPARISON OF THREE DOPPLER METHODS IN THE PREDICTION OF PULMONARY ARTERY PRESSURE.

Kwan-Leung Chan, M.D., Philip J. Currie, M.B.,B.S., James B. Seward, M.D., F.A.C.C., Donald J. Hagler, M.D., F.A.C.C., Douglas D. Mair, M.D., F.A.C.C. and A. Jamil Tajik, M.D., F.A.C.C., Mayo Clinic, Rochester, MN.

The three Doppler methods used in 50 consecutive patients undergoing cardiac catheterization were: (i) systolic tricuspid gradient (calculated from Doppler-detected tricuspid regurgitation) plus clinical jugular venous pressure or a constant of 14 mm Hg, to yield systolic PA pressure; (ii) acceleration time from PA flow analysis in a regression equation to derive mean PA pressure; and (iii) RV isovolumic relaxation time (RT) (derived from Doppler-determined pulmonary closure and tricuspid opening) used in a nomogram to give systolic PA pressure. In 48 patients (96%), at least 1 of the 3 methods could be applied. Tricuspid gradient was obtained in 36 patients (72%). The tricuspid regurgitation velocities ranged from 2.0 to 4.5 m/s, with a mean of 2.9. Systolic PA pressure prediction was superior when 14 mm Hg was used to account for RA pressure ($r = 0.87$). In 44 patients (88%) PA flow contour was obtained; 12 of the 44 did not have Doppler-detected tricuspid regurgitation. Prediction of mean PA pressure was unsatisfactory ($r = 0.65$) but improved when only patients with heart rates between 60 and 100 beats/min were considered ($r = 0.85$). Determination of RT was feasible in only 11 patients (22%), due to high incidence of arrhythmia. In this subset the prediction was acceptable ($r = 0.83$). Thus, noninvasive prediction of PA pressure by Doppler is feasible in most patients and, of these 3 methods, the tricuspid gradient method appears to be the most useful.

SONOSPIROMETRY: A NON-INVASIVE METHOD FOR ESTIMATING RIGHT ATRIAL PRESSURE

Jay S. Simonson, M.D., Robert H. Merz, M.D., Nelson B. Schiller, M.D., F.A.C.C.

Knowledge of mean right atrial pressure (RAP) is useful for evaluation of right heart hemodynamic status and for calculation of pulmonary pressures by Doppler. However, a non-invasive method for accurate, reliable estimation of this pressure does not exist. To estimate RAP we used a Bourdin pressure gauge with a 14ga bleed-off port to measure voluntary inspiratory pressures and supine 2-D echocardiographic long axis imaging of the inferior vena cava (IVC) from a subxiphoid window to quantitate the diameter of the IVC. Thirteen alert and cooperative patients (8 males) ranging in age from 36 to 79 were studied on 15 occasions. All patients had pulmonary artery pressure catheters in place during the study. RAP was measured from RA tracings immediately following each study. RAP ranged from 0 to 15mmHg in the patients studied. IVC diameters were measured at the narrowest point 2 to 7 cm from the RA-IVC junction. The IVC diameter was measured during a series of constant inspiratory pressures at 5cmH20 (4mmHg) increments. The maximum IVC diameter was determined while the patient held a full breath. The minimum obtainable IVC diameter was determined from the minimum measurement during the study of each patient. The minimum inspiratory pressure required to collapse the IVC diameter to 75% or more of the difference between the maximum and minimum IVC diameter was found to be equal to the RAP (r=0.90). The method is accurate to ±2mmHg over a RAP range of a least 0 to 15 mmHg. The upper limit of RAP determination using this method remains to be defined. Sonospirometry is a useful method for non-invasive estimation of RAP.

PULSED DOPPLER HEPATIC VEIN BLOOD FLOW IN TRICUSPID REGURGITATION AND ATRIAL SEPTAL DEFECT

Ali Dabestani, MD, Katsu Takenaka, MD, Walter L Henry, MD, FACC. University of California, Irvine, California.

Doppler hepatic vein flow has been shown to be useful in the diagnosis of tricuspid regurgitation (TR). Atrial septal defect (ASD) and TR both can produce large end-systolic retrograde v-flow, thus making differentiation difficult. To separate ASD from TR, we studied hepatic vein flow velocity using pulsed Doppler echocardiography in 7 normals, 8 patients with TR and 7 with ASD. Peak flow velocities of antegrade (i.e. toward the heart) systolic and diastolic flow, and retrograde end-systolic v-flow velocity (i.e. away from the heart and toward the liver) were measured in cm/sec. Interval from the onset of Q wave of ECG to the peak of v-flow was measured in milliseconds (Q-v). Results for both respiratory phases are (mean ± SD):

	Diast. Flow		v Flow		Q-v	
	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.
Normal (n=7)	15± 6	13±3	19± 8	11± 4	451±54	466±54
TR (n=8)	51±28*	27±8*	39±17*	20±12	354±52*	361±56*
ASD (n=7)	19± 7	11±7	14±11	29±16*	407±73	405±61

* $p < 0.05$ compared to normal values

Antegrade systolic flow velocity was similar among the 3 groups. Antegrade diastolic flow velocity throughout respiration and retrograde v-flow velocity only in inspiration was significantly increased in TR compared to normals and ASD. In addition, v-flow velocity increased during inspiration in both TR and normals but decreased in ASD ($p < 0.05$). Q-v interval was significantly shortened in TR compared to normals. We conclude that prematurity and distinct respiratory behavior of v-flow as well as increased diastolic flow can distinguish tricuspid regurgitation from atrial septal defect.

TRICUSPID REGURGITATION IN NORMAL SUBJECTS: PREVALENCE AND POSSIBLE MECHANISM.

John J. Lynch, M.D., Kiran B. Sagar, M.D., F.A.C.C., L. Samuel Wann, M.D., F.A.C.C., Medical College of Wisconsin, Milwaukee, Wi.

Doppler echocardiography frequently detects tricuspid regurgitation (TR) in normal subjects. To determine the prevalence and possible mechanism of tricuspid regurgitation in normal subjects we performed two-dimensional and pulsed Doppler echocardiography in 30 normal volunteers. All subjects also underwent history, physical examination and electrocardiogram. Diagnosis of tricuspid regurgitation was made if a turbulent systolic flow was detected in the right atrium below the tricuspid valve. Measurements of tricuspid valve annulus diameter at end-diastole (TVD), right ventricular diameter at end-diastole (RVD), right atrium (RA) length and width at end-systole were made from the apical four chamber view. These were indexed to body surface area. Tricuspid regurgitation was present in 16 of 30 subjects (53.3%). Subjects with tricuspid regurgitation had greater RA length, RA width, and RVD than those without. TVD was similar in the two groups.

	RA Length [Mean + SD]	RA Width	RVD	TVD
TR Present (16 subjects)	2.42±.42*	2.03±.45*	2.03±.48*	1.77±.45
TR Absent (14 subjects)	2.02±.42	1.72±.33	1.7 ±.35	1.49±.28

* $p < .05$ + values are cm/m^2

We conclude that prevalence of TR in normal subjects is quite high and it may represent a mismatch in RA, right ventricle and tricuspid valve annulus.

SIGNIFICANCE OF LAMINAR SYSTOLIC TRICUSPID REGURGITANT FLOW IN PATIENTS WITH TRICUSPID REGURGITATION: DOPPLER AND ECHOCARDIOGRAPHIC STUDY.

Shinichi Minagoe, MD, Charles R McKay, MD,FACC, Shahbudin H Rahimtoola, MD,FACC, P Anthony N Chandraratna, MD,FACC LAC-USC Medical Center, Los Angeles, CA.

In order to define the cause & significance of laminar systolic tricuspid regurgitant flow, pulsed & continuous wave Doppler (PWD,CWD), two-dimensional and M-mode echocardiography (2DE, M-mode) were performed in 67 patients (pts) with tricuspid regurgitation (TR) which included 5 pts with tricuspid valvectomy (TVT). TR flow pattern (laminar or turbulent), TR severity by detecting the extension of TR in the right atrium(1+ to 4+) by PWD, the peak flow velocity of TR (PFV) by CWD and the systolic pressure gradient (PG) across the tricuspid valve derived by using modified Bernoulli's equation ($\Delta P=4V^2$; $\Delta P=PG$, V=PFV), presence and distance of systolic tricuspid cusp separation (STCS) by 2DE, & the dimension of the right ventricle (RVD) by M-mode were assessed. Results:

TR flow	N	PFV (m/sec)	PG (mmHg)	STR (4+)	STCS (+)	STCS (-)	TVT	RVD (mm)
Laminar	21	2.0±.7	17±11	14/21	14	2	5	38.2±9.4
Turbulent	46	3.1±.7	40±18	4/46	0	46	0	24.7±9.5

STR= Severe TR *p<.001

The distance of STCS(tricuspid annulus in pts with TVT) ranged from 3 to 40mm & was inversely correlated with the log of PFV (r=-.94, SEE=.1m/s, p<.001) or the log of PG (r=-.94,SEE= .3mmHg, p<.001) in 19 pts with laminar flow. CONCLUSION: Laminar systolic TR flow,low PFV of TR & low PG in systole, occur in many pts with severe TR. These features are probably due to a large regurgitant orifice as evidenced by their association with STCS or TVT. Therefore, the presence of systolic laminar TR flow is strongly suggestive of the presence of severe TR.

INCIDENCE OF VALVULAR DYSFUNCTION IN METASTATIC CARCINOID SYNDROME: UTILITY OF DOPPLER AND COLOR FLOW MAPPING.
Bijoy K. Khandheria, M.D., A. Jamil Tajik, M.D., F.A.C.C., Mark J. Callahan, M.D., John A. Callahan, M.D., F.A.C.C., Rick A. Nishimura, M.D., F.A.C.C., Charles G. Moertel, M.D. and James B. Seward, M.D., F.A.C.C., Mayo Clinic, Rochester, MN.
The characteristic structural abnormalities of carcinoid heart disease have been well described by two-dimensional echocardiography (2DE). Doppler detection of valvular dysfunction in this entity has not been reported. We studied 27 pts (20 M, 7 F; mean age 67 yr, range 30-72 yr) with documented metastatic carcinoid syndrome. 2DE revealed thick, retracted tricuspid leaflets in 17 (63%); Doppler examination revealed tricuspid regurgitation (TR) in 21 (78%) with an average peak jet velocity of 2.5 m/s (range, 1.8-3.0 m/s). Continuous-wave Doppler in 13 pts revealed tricuspid stenosis in 8 (62%). The average peak antegrade velocity across the tricuspid valve was 1.3 m/s (range, 1.1-2.0 m/s) and the diastolic half-time ranged from 70-170 ms. Pulmonary regurgitation (PR) was detected in all 11 who had optimal Doppler signals; 3/11 (27%) had evidence of pulmonary stenosis (1.4, 1.8, and 3.0 m/s) and a thick pulmonary cusp visualized on 2DE. On color flow imaging performed in 5 recent pts, moderate TR was found in 4 and mild in 1. A jet configuration consisting of a central blue zone surrounded by shades of red and yellow--indicative of color reversal (aliasing)--was seen in 4 (80%); PR was seen in 3 (60%). Conclusion: 1. The incidence of TR and PR is high in carcinoid heart disease. 2. Associated tricuspid stenosis is present in 61%. 3. Color flow imaging permits definition of regurgitant jet configuration and semiquantitation of regurgitation. Combined 2DE and Doppler examination provides a comprehensive assessment of valvular dysfunction in metastatic carcinoid syndrome.

APPLICATION OF ANNULAR PHASED ARRAY TECHNOLOGY TO TWO-DIMENSIONAL ECHOCARDIOGRAPHIC IMAGING
Thomas Ryan, M.D., Charles G. Vasey, M.D., William F. Armstrong, M.D., F.A.C.C., Harvey Feigenbaum, M.D., F.A.C.C.; Indiana University School of Medicine, Krannert Institute of Cardiology; Indianapolis, Indiana
Annular phased array (AA) ultrasonic transducers have only recently become available for cardiac imaging. These mechanically oscillating transducers, which consist of multiple elements aligned in concentric rings, permit adjustable focusing of the ultrasonic beam and result in significantly thinner tomographic slices. Although the advantages of AA transducers, which include improved lateral resolution, increased signal-to-noise ratio, and better penetration, are known, the potential role of this technology in cardiac imaging remains largely unexplored. We studied 30 adults with both conventional and AA (ATL Ultramark 8) transducers. The improved penetration of the AA system permitted the use of higher frequency transducers (3.5 and 5.0 MHz) than was possible with conventional systems. This resulted in increased resolution, better definition of endocardial borders, and improved recording of fine structures, such as valve leaflets, chordae tendineae, and coronary arteries. The AA transducer was particularly helpful in excluding the presence of intracardiac masses in cases where conventional systems provided equivocal results. In 3 cases in which the presence of intracardiac thrombus (2 LV, 1 LA) could not be resolved using a conventional system, the AA system provided an unequivocal diagnosis. The AA transducer was useful in excluding the presence of small valvular vegetations, permitted detection of a small primum ASD, and allowed diagnosis of a flail mitral valve, none of which were correctly diagnosed with conventional transducers. In conclusion, AA technology is a significant advance in ultrasonic cardiac imaging.

Wednesday, March 12, 1986
10:30AM-12:00NOON, Room #313/314
New Echocardiographic Technology

"SILENT" ATRIAL SEPTAL DEFECTS FOUND BY CONTRAST ECHOCARDIOGRAPHY ARE HIGHLY ASSOCIATED WITH EMBOLIC STROKE
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Two-dimensional echocardiography (2DE) is said to be of minimal value in the evaluation of cardiac source of cerebral embolization when the cardiac physical exam, chest radiograph, and ECG are all normal. In the past year, 16 patients age 50 or younger fulfilled these criteria, had normal 2DE examinations, and clinical and radiographic evidence for cerebral embolization. During normal respiration, 10 of 16 had positive findings for right-to-left shunts at the atrial level by microcavitation contrast 2DE. Lung scans were positive in 1 of 6, but venography was negative. Five of the ten with positive contrast 2DE studies underwent cardiac catheterization. All five had an atrial defect, normal right and left heart pressures, and small left-to-right shunts (maximun 1.4 : 1). All had right-to-left shunts by indicator dye curves during a valsalva strain. Four of the five (ages 18, 29, 41 and 50) underwent surgical closure of the defect, which ranged from 5 to 15mm in diameter and was classified as a patent foramen ovale (3) or a secundum atrial septal defect (1). The remaining patients received anticoagulants. These findings suggest: 1)Widely patent foramen ovale and atrial septal defects are commonly found in young patients with cerebral emboli, making paradoxical embolization possibly more common than expected. 2)Contrast 2DE is the only noninvasive technique that reliably finds these defects. 3)Contrast 2DE should be routinely performed in young patients with stroke.

ASSESSMENT OF LEFT VENTRICULAR EJECTION FRACTION FROM CONTRAST ECHO WASHOUT CURVES: A NEW METHOD INDEPENDENT OF GEOMETRIC ASSUMPTIONS
Daniele Rovai, M.D., Steven E. Nissen, M.D., Oi Ling Kwan, Anthony N. DeMaria, M.D., FACC; University of Kentucky and VA Medical Center, Lexington, Kentucky
In previous studies we have demonstrated that the decay phase of time-intensity curves derived from contrast echocardiography(CON) of the left ventricle is monexponential. Therefore, this study was performed to develop a method for calculation of LV ejection fraction by analysis of the decay phase of such curves. We performed CON by injecting 3 ml boluses of the saccharide contrast agent SHU454 into the left ventricle. An independent measurement of ejection fraction was obtained by area-length analysis of digital subtraction left ventriculograms. Data were obtained in 6 closed chest mongrel dogs at 31 different levels of ejection fraction which were created by changes in preload (volume), afterload (methoxamine) and contractility (dobutamine). CON were recorded in the apical 4-chamber view, were digitized off-line, and the mean gray level/pixel in the LV cavity was measured before, during, and after contrast appearance. The pixel values from the 2nd to 4th systolic frame of each beat were averaged, and the resultant intensities plotted against time to yield a rectilinear decay phase. Multiple linear regression analysis indicated that LV was related to the slope and peak of the time-intensity curves, as well as to the mean duration of the cardiac cycle. An index was therefore devised to account for these variables. Linear regression analysis of this index and angiographic ejection fraction yielded a correlation of r=0.83. Thus, these data indicate that analysis of the decay phase of time-density curves obtained from contrast echocardiography can be utilized to provide estimates of LV ejection fraction without geometric assumptions. Values on ejection fraction calculated by contrast echo correlate well with those of angiography.

EFFECT OF REGIONAL ISCHEMIA ON DIASTOLIC LEFT VENTRICULAR INTRACAVITARY FLOW VORTEX - COLOR DOPPLER AND CONTRAST ECHOCARDIOGRAPHIC STUDIES.

Natesa Pandian, M.D., John Funai, M.D., Shan Shen Wang, M.D., Barbara Lowell. Tufts-New England Medical Center, Boston, Massachusetts.

To assess the effect of regional ischemia and left ventricular (LV) dysynergy on diastolic LV intracavitary flow dynamics, we used two-dimensional color Doppler and saline contrast echocardiography in 9 dogs in control and during 20 instances of ischemia created by occlusion of left anterior descending or circumflex coronary arteries. From two-dimensional color Doppler images we analyzed the pattern, direction and distribution of flow jets within the LV cavity. We measured the width of antegrade diastolic inflow (ADF) and retrograde diastolic vortical flow (RVF) in controls and during ischemia and calculated ADF/RVF ratios. From saline contrast echocardiographic images the diastolic motion of contrast bubbles was analyzed during washout phase. Results: During all controls, a definite normal flow vortex formation was noted during diastole with the RVF predomonantly in the anterior portion of LV. ADF/RVF ratio in control was 5.3±1.4. During ischemic LV dysfunction however ADF/RVF ratio decreased strikingly to 1.4±.25 ($p<.01$). On saline contrast echocardiography a swirling of flow was noted during ischemia; it was more prominent in the presence of anteroapical ischemia or when the ischemic zone was larger. These findings indicate that regional ischemia alters the diastolic left ventricular intracavitary flow dynamics with enhanced tendency for vortex formation and favoring regional stasis.

DIGITAL ECHOCARDIOGRAPHIC VISUALIZATION OF THE LEFT CORONARY ARTERIES USING AN ANNULAR PHASED ARRAY SYSTEM

Charles G. Vasey, M.D., Thomas Ryan, M.D., William F. Armstrong, M.D., F.A.C.C., Harvey Feigenbaum, M.D., F.A.C.C.; Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis, Indiana

Annular array (AA) systems for cardiac imaging have recently been developed. AA utilizes a mechanically oscillating transducer with circular elements which electronically focus the beam in both the X and Y axes. This results in improved lateral resolution (< 1 mm in vitro) and thinner tomographic slices, allowing for the first time in an adult the direct visualization of a non-dilated coronary artery (CA) lumen beyond the left main. We examined the left CA in 34 patients (pts) using a 5 MHz AA transducer (ATL Ultramark 8). The arteries were visualized in the short-axis plane and magnified using a digital zoom. CA images were then captured off-line (Microsonics analyzer) at 50 msec intervals in an 8 cell digital format that enabled construction of a continuous loop playback of only the CA. AA allowed visualization of the left main CA in 33 pts, including its bifurcation in 29. The lumen of the left anterior descending was visualized in 29 pts; in 4 a proximal branch was also seen. The left circumflex was seen in 22 pts, once including the origin of the first marginal. High intensity echoes corresponding in location to lesions observed cineangiographically were seen in the left main in 4 pts, at its bifurcation in 1 pt, in the proximal left anterior descending in 4 cases, and twice in the circumflex. Initial experience therefore suggests that the enhanced resolution resulting from annular array technology, together with improved digital analysis, is an important ultrasonic advance that may prove to be of considerable clinical utility in examining the left coronary arteries.

ECHOCARDIOGRAPHIC CONTRAST PERSISTENCE IS DEPENDENT ON INJECTATE AND BLOOD TEMPERATURE.

Christopher R. Thompson, M.D., Rosalind P. MacDonald, B.Sc., John V. Tyberg, M.D., Ph.D., F.A.C.C. and Eldon R. Smith, M.D., University of Calgary, Calgary, Canada.

Clinical use of echocardiographic contrast (C) to study myocardial perfusion will depend on production of microbubbles of known size and persistence (PERSIST). Previous assessments of bubble size have been made at room temperature (TEMP). In 7 dogs, we obtained excellent myocardial C enhancement without significant hemodynamic alteration following 42 coronary injections of mechanically and sonically agitated 30% dextrose in water (D30) but noted marked variation in C PERSIST. To determine if this variation could reflect uncontrolled injectate (INJ) TEMP, we evaluated the TEMP dependence of C PERSIST using echocardiographic images of rate and pressure-controlled 3 ml injections of 3 C agents [agitated D30 and D70 and 1:1 agitated Renografin-76/saline (R/S)] into a balloon containing dog blood (BLD). The mean of PERSIST estimates by 2 observers following 6 injections at each of 3 TEMPs were:

TEMP(°C)		PERSISTENCE (secs) ± 1 SD		
INJ	BLD	D30	D70	R/S
21°	21°	112±35	287±61	292±22
21°	37°	524±148†	1001±243†	1063±118†
37°	37°	195±99†	389±127*	461±219†

* = $p<.05$, † = $p<.005$ vs same agent at 21°/21°

In this in vitro model C PERSIST is markedly longer at 37° than at 21°. Since larger bubble size may be the major factor in prolonged C PERSIST, we conclude that: 1) TEMP of INJ is an important, controllable variable in echocardiographic myocardial perfusion studies; 2) use of cold INJ for in vivo studies may produce larger bubbles than previously appreciated.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #264/265/266
Ventricular Function

VENTRICULAR VOLUMES, SYSTOLIC AND DIASTOLIC FUNCTION IN ACUTE MYOCARDIAL INFARCTION: RELATION TO INFARCT SIZE AND LOCATION

A. Allen Seals, M.D., Sameh Tadros, M.D., Craig M. Pratt, M.D., F.A.C.C., Robert Roberts, M.D., F.A.C.C., Mario S. Verani, M.D., F.A.C.C. Baylor College of Medicine, Houston, TX.

To date, quantification of LV volumes and diastolic function in the initial hours of acute infarction has not been done. Accordingly, in 62 patients with acute myocardial infarction (anterior n = 34, inferior n = 28) on day 1 of infarction, we performed high-framing rate radionuclide angiography and assessed LV end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), ejection fraction (EF), peak systolic pressure-volume index (PSP/ESVI) and peak diastolic filling rate (PDFR). Infarct size was calculated from serial CK-MB curves. Studies were repeated on day 10 post-infarction in 16 patients.

RESULTS (M ± SD):	ANTERIOR	INFERIOR	P
EF(%)	46±15	52±14	ns
EDVI(ml/m²)	107±41*	76±21	< .001
ESVI(ml/m²)	61±40*	38±21	< .01
SVI(ml/m²)	46±15*	38±10	< .05
PSP/ESVI(mmHg/ml)	1.6±1.2	2.1±1.2	ns
PDFR(EDV/s)	2.1±.6	2.1±.8	ns
INFARCT SIZE(CK·g·Eq)	35±16*	19±7	< .002

On repeat study, EDVI and ESVI further increased ($p <$ .05 vs day 1), although EF, PSP/ESVI, and PDFR were unchanged. Conclusions: 1) The LV dilates markedly within hours in patients with anterior infarction, but only minimally with inferior infarction 2) In contrast, diastolic function was impaired to a similar extent in both, and 3) Despite extensive myocardial damage, stroke-volume was maintained by left ventricular dilatation.

CORONARY ANGIOGRAPHIC AND LEFT VENTRICULAR ABNORMALITIES ASSOCIATED WITH RIGHT VENTRICULAR INFARCTION

Simon Kouz, M.D., Pierre Théroux, M.D., F.A.C.C., Sébastien Roux, M.D., David D. Waters, M.D., F.A.C.C., Denis Roy, M.D., F.A.C.C. and Georges Dupras, M.D., Montreal Heart Institute, Quebec, Canada

Equilibrium gated radionuclide ventriculography was performed during the acute phase of inferior myocardial infarction in 128 pts who were catheterized 10±3 days after admission. All pts without contraindications underwent arteriography. Right ventricular involvement (RVI), diagnosed by RV dilatation or RV wall motion abnormality was observed in 37 pts (29%). The right coronary artery (RCA) was dominant in 36 of 37 pts with RVI and in all 16 with RVI and 1 vessel disease. ST depression in the anterior ECG leads at admission was seen in 21 pts (57%) with RVI vs 43 (47%) without (p=NS).

	RVI	no RVI	p
Peak CPK (IU/L)	2344±301	1689±148	<.02
Q wave MI	32 (86%)	64 (70%)	NS
LVEF	53±9	52±10	NS
Posterobasal akinesis	29 (78%)	52 (57%)	<.05
Diaphragmatic akinesis	24 (65%)	46 (51%)	NS
1 vessel disease	16 (43%)	22 (24%)	<.05
3 vessel disease	6 (16%)	29 (32%)	<.05
Proximal RCA ≥70%	28 (76%)	54 (59%)	NS
Proximal RCA ≥90%	26 (70%)	40 (44%)	<.05
RCA stenosis ≥99%	27 (73%)	44 (48%)	<.05

We conclude that radionuclide-detected right ventricular involvement in inferior myocardial infarction implies total occlusion or severe proximal stenosis of a dominant right coronary artery usually with posterobasal akinesis. Higher enzymes reflect associated right ventricular damage. In patients with right ventricular involvement who survive to arteriography, 3 vessel disease is uncommon.

CAN THE DEGREE OF REGIONAL SHAPE DISTORTION ON AN EARLY TWO-DIMENSIONAL ECHOCARDIOGRAM AFTER MYOCARDIAL INFARCTION IDENTIFY PATIENTS PRONE TO INFARCT EXPANSION?

Bodh I. Jugdutt, M.B.,F.A.C.C., Univ.of Alberta, Edmonton.

To determine whether the extent of regional shape distortion (SD) on an early two-dimensional echocardiogram (2DE) after myocardial infarction can predict infarct expansion, serial clinical and 2DE data were recorded between 2 and 10 days after acute transmural infarction in 242 consecutive patients (113 anterior, 129 inferior). Regional LV asynergy (akinesis and/or dyskinesis), regional SD, and anterior and posterior segment lengths were measured in endocardial diastolic outlines of papillary or chordal 2DE sections.More than 25% stretching and thinning of asynergic segments (AS) was found between 2 and 10 day 2DE studies in 50 expanders (acute LV dilatation and failure; no new ECG or creatine kinase changes). The new SD index, (Pk or peak of the angular distribution between the distorted asynergic segment and the computed ideal segment of a circle), but not the traditional SD index ($P^2/4\pi A$; P=perimeter, A=area),was markedly different in expanders than non-expanders at 2 and 10 days.

	Expanders(n=50)	Non-Expanders(n=192)
$P^2/4\pi A$:2 day	1.09	1.06
Pk(mm):2 day	14.00*	9.70
Δ% AS length:7 day	53.2*	3.8
Δ% AS thickness:7 day	-27.8*	-6.2
Killip class(maximum)	3.3*	2.4
Deaths (2-10 day)	14(28%)**	15(8%)

* P < 0.05 (ANOVA); ** X^2 = 13.5, P < 0.001

All expanders had Pk>10mm and AS>15% on the 2DE at 2 days. Also,10 expanders with >30% increase in Pk (to 21 mm) developed ventricular septal defects (n=8) or cardiac rupture (n=2). Thus, the degree of SD on a 2DE at 2 days can identify expanders and those with higher morbidity.

DYSKINESIS, BUT NOT AKINESIS, PREDICTS THE PRESENCE OF LEFT VENTRICULAR THROMBUS IN ACUTE ANTERIOR MYOCARDIAL INFARCTION.

Gervasio A. Lamas, M.D., Douglas E. Vaughan, M.D., and Marc A. Pfeffer, M.D., Ph.D., FACC. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Left ventricular thrombus (LVT) is an early complication that occurs in some patients following acute anterior myocardial infarction (AAMI). To determine the factors associated with the development of LVT, hemodynamic and angiographic features were assessed in 39 patients undergoing left ventriculography 14 to 28 days following AAMI. The extent of the non-contractile segment (A+D) was defined as the percent of the end-diastolic perimeter that was akinetic (A) and/or dyskinetic (D). This infarcted segment (A+D) was partitioned further into regions which were either solely A or D. Over a wide range of infarct sizes, A and D were found to vary independently of each other. As expected in AAMI, LVEDP, EF, systolic and diastolic volumes, and stroke index were all highly related (P<0.01) to A+D. Angiographic LVT was found in 18/39 (46%) of the patients. The incidence of LVT increased significantly (P<0.01) as A+D increased.

A+D (%)	< 20	21-30	> 31
incidence LVT	2/12 (17%)	3/8 (38%)	13/19 (68%)

Of the components (A,D) of the infarcted segment, only D was found to correlate (P<0.01) with the presence of LVT.

D(%)	< 10	10-19.9	> 20
incidence LVT	2/14 (14%)	8/12 (67%)	8/13 (62%)

In patients with AAMI and an extensive infarcted segment with a large D component, there is a 4 fold increase in the incidence of LVT compared to patients with a small D component. This relationship between the extent of dyskinesis and the presence of thrombus is not observed for comparable degrees of akinesis, suggesting that systolic bulging is an important component of thrombus formation.

SILENT VS SYMPTOMATIC ISCHEMIA ON EARLY POST-INFARCTION TREADMILL TESTING: ANGIOGRAPHIC CHARACTERIZATION AND 1 YEAR FOLLOW-UP

Pamela Ouyang, M.D., Edward P. Shapiro, M.D., F.A.C.C., Nisha C. Chandra, M.D.,Sheldon H. Gottlieb, M.D., Paul H. Chew, M.D. and Sidney O. Gottlieb, M.D., The Johns Hopkins Medical Institutions. Baltimore, Maryland

To determine if post-infarction patients (pts) with silent (SIL) or symptomatic (SX) ischemia on early exercise treadmill testing (ETT) differ in angiographic charateristics or 1 year follow-up, we studied 60 consecutive pts with positive pre-discharge Naughton ETT (≥1 mm ST shift or typical angina symptoms) who underwent coronary angiography 24±4 days post-MI. Ischemia was silent in 63% (38/60). Age, sex and use of beta-blockers, calcium antagonists and nitrates at the time of the ETT did not differ in the two groups (gps). All 9 pts with diabetes mellitus were in the SIL gp (p<.04). ETT did not differ between gps in total duration (SIL=422±31 sec, SX=400±46 sec), in workload expressed as HR X BP, in pts unable to exercise 5 mins (12 SIL, 7 SX), in pts with diffuse ECG changes (9 SIL, 7 SX) or in pts with ischemic ECG changes distant from the MI zone (SIL 28, SX 12). Severity of coronary artery disease (CAD) did not differ between gps in mean number of coronary arteries with ≥70% stenosis (2.0±0.2 SIL, 2.2±0.2 SX), or in number of pts with ≥2 vessel CAD (74% SIL, 73% SX), left main CAD (4 SIL, 1 SX), or total occlusion of the infarct related artery (66% SIL, 55% SX pts, p=NS). Over 1 year follow-up in 92% of pts, 4 SIL (11%) and 1 SX (5%) pts had cardiac death or recurrent MI (NS) and 17 SIL (45%) and 13 SX (59%) pts underwent revascularization with bypass surgery or angioplasty (NS). Thus, SIL ischemia occurs frequently on early post-infarction ETT; the angiographic characteristics and 1 year outcomes of these pts are similar to pts with SX treadmill ischemia.

CLINICAL CORRELATIONS AND LONG-TERM PROGNOSIS AFTER UNCOMPLICATED NON Q-WAVE INFARCTION: A PROSPECTIVE NATURAL HISTORY STUDY. Robert S. Gibson MD, Denny D. Watson PhD, Sharon L. Sayre RN, BSN, Mihai Georghiade MD, FACC, George A. Beller MD, FACC. Univ. of Virginia, Charlottesville, VA

Despite a smaller infarct size and better LV function, pts with non Q-wave(NQ) MI appear to have a prognosis comparable to QMI. One explanation is that there is more residual viable tissue in the perfusion zone of the infarct vessel rendering myocardium more prone to reinfarction. Accordingly, we prospectively studied 241 consecutive pts (age≤65yrs) with MBCK confirmed acute MI. Predischarge angiography(angio), radionuclide ventriculography, exercise (Ex)Tl-201 scintigraphy and 24 hr Holter was performed 10± 3d post-MI. Infarcts were designated NQMI(n=88) or QMI(n=153) by serial ECGs(d1,2,3 and 10). Norris index and angio jeopardy scores were similar despite less necrosis with NQMI vs QMI, reflected by lower peak CK(553vs1321,p<.001; 4 hr sampling), higher LVEF(53vs46%,p<.001), fewer akinetic or dyskinetic LV segs(1.3vs2.4,p<.001), and fewer persistent Tl-201 defects(0.9vs1.9,p<.001). Compared to QMI pts, NQMI had more patent infarct vessels(25vs53%,p<.001) and a shorter time to peak CK(23vs17hrs,p<.001). Importantly, the prevalence and extent of Ex-induced ischemia within the infarct zone by quantitative Tl-201 was greater in NQMIvsQMI(60vs36%,p<0.001; and 0.98vs0.53 segs,p<.001). During 29 mos follow-up, cardiac mortality was 9% in both groups. However, NQMI pts had a higher reinfarction rate (17%vs6.5%,p=.02) and greater likelihood of subsequent CABG surgery(33%vs18%,p=0.017). Thus, in a consecutive series of uncomplicated MI pts, NQMI is characterized by equal mortality despite better LV function, a higher recurrent MI and CABG rate at 29 mos, and more evidence for residual infarct zone ischemia compared to QMI pts. Also, our data suggest that the pathogenesis of NQMI may involve spontaneous reperfusion.

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #264/265/266
Percutaneous Transluminal Angioplasty

EMERGENCY PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION. Donald A. Rothbaum,MD,FACC, Thomas J. Linnemeier, MD, FACC, R. Joe Noble, MD, FACC,St. Vincent Hospital, Indianapolis, IN.

Angioplasty (PTCA) was evaluated as primary therapy for acute myocardial infarction(MI) in 75 patients(pts). All had ECG changes for MI and normal or minimally elevated cardiac enzymes (less than twice normal) prior to PTCA. Cardiogenic shock(CGS) was present in 9 pts, all with LAD occlusion. Followup was 6-24 months.

Subtotal vessel occlusion (SO) of 90-99% was found in 25 pts (33%), total occlusion (TO) in 50 pts (67%). PTCA was performed in less than 3 hours after initial ECG. The results are summarized:

Lesion %	LAD	RCA	LCX	Total (%)	Avg.	(Range)
(90-99%)	12/12	9/9	4/4	25/25 (100%)	32%	(0-50%)
(100%)	19/23	14/17	9/10	42/50 (84%)	33%	(0-70%)

Combined success rate was 89% (67/75 pts). In the TO pts, unsuccessful PTCA was due to failure to cross the lesion in 5 pts and thrombotic reocclusion in 3 pts.

Total mortality was 6.3% (5/75 pts). All deaths occurred in pts with CGS, 4 died acutely and 1during followup. Acute vessel reclosure occurred in 2 pts, 1 had successful re-PTCA, the other had CABG.

Repeat angiography was performed (>3 months post PTCA) in 46 pts. Regional wall motion was improved ≥ 20% in 28 pts (61%); 12/15 SO, 16/31 TO. A widely patent vessel was found in 31/46 pts (67%). Restenosis (≥50% occurred in 8 pts(17%) 7 had successful PTCA and 1 had CABG. Reocclusion occurred in 7 pts (15%) but all occluded vessels had good collateral fill and no pts experienced late reinfarction. CABG was performed in a total of 6 pts, 2 acutely and 4 during followup.

In summary, emergency PTCA during acute MI was performed with a high initial success rate and a low overall mortality confined exclusively to pts presenting in cardiogenic shock.

DIRECT BALLOON ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION: WITHOUT PRIOR USE OF STREPTOKINASE Barry D. Rutherford, MD FACC, Geoffrey O. Hartzler MD FACC, David R. McConahay, MD FACC, Warren L. Johnson Jr. MD FACC. Mid America Heart Institute at St. Luke's Hospital, Kansas City, Missouri.

Direct percutaneous transluminal coronary angioplasty (PTCA) was performed during acute myocardial infarction (AMI) in 222 patients (pts). One hundred and seven pts had anterior AMI, and 115 pts inferior AMI. Q-waves were present in 78 pts (35%) prior to direct PTCA. Catheterization was performed from 1-24 hours following the onset of symptoms, mean time from pain onset to patent artery was 4.5 hours (range 1-24 hours). Single vessel coronary disease was found in 96 pts (43%), double or triple vessel disease (TVD) in 126 pts (57%). One hundred and thirty-two pts (60%) had complete occlusion of the infarct vessel, 90 pts (40%) had 75-99% stenoses. Angiographic thrombi were noted in 57% of pts; 16% had collaterals to the infarct artery.

Initial successful PTCA was obtained in 203 pts (91%); total in-hospital mortality was 7%. Twenty-three pts (10%) reoccluded the infarct artery in the post-PTCA period, six pts developed early restenosis. Seventeen pts (7%) went to saphenous vein bypass grafting, 9 pts because of failed PTCA, 8 pts due to severe TVD.

One hundred and eighty-two pts (82%) were entirely stable at the time of dismissal. Follow-up studies were obtained in 123 pts at a mean period of 10 days. One hundred (81%) of dilated arteries had remained patent, and in these pts the mean ejection fraction improved from 47% prior to PTCA to 59% after PTCA.

We conclude that direct PTCA in AMI provides: 1) Rapid total patency of the infarct artery in a majority of pts (91%); 2) Maintained patency of the artery in the early post-PTCA period; 3) Improved LV function.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN CARDIOGENIC SHOCK

Jacob Shani, M.D., Marcos Rivera, Alvin Greengart, M.D.,F.A.C.C., Gerald Hollander, M.D., F.A.C.C., Paul Kaplan, Edgar Lichstein, M.D., F.A.C.C., Maimonides Medical Center, SUNY, Downstate Medical Center, Brooklyn, N.Y.

Successful coronary angioplasty (A) was performed in 6 of 9 patients (pts) with acute myocardial infarction (MI) complicated by cardiogenic shock (CS). A was performed 60-190 minutes (mean 140) after the onset of symptoms. Three pts required a double vessel A, all had intra aortic balloon pump insertion prior to A. The infarct related artery was the LAD in 7 pts, a dominant RCA in 1 and a dominant LCX in another. There were 6 males and 1 female with a mean age of 58.7 (range 39-73). Five pts had a previous MI.

Hemodynamics

	Pre A	Post A	3-6 Months
PCWP mm/Hg	17-31 (24.8)	16-26 (21.3)	8-19 (14)
LVEDP mm/Hg	23-40 (31.6)	20-27 (24.7)	16-23 (19.8)
BP mm/Hg	60-81 (71)	90-105 (94)	105-130(117)
HR BPM	96-144 (127)	92-110 (103)	68-92 (79)
CI L/min/sq.M	1.2-1.6 (1.4)	1.8-2.1 (1.9)	1.8-2.4(2.2)
EF		.27-.41(.36)	.38-.57(.48)

All hemodynamic changes were significant ($p < .01$). Three pts died in the catheterization laboratory. Coronary angiography 3-6 months post A revealed patent arteries in 5 pts. There was dramatic clinical improvement immediately after A. At follow-up 5-16 months (mean 9.5) post A, 5 of the 6 survivors are symptom free and employed. We conclude that A can be performed successfully in pts with MI and CS.

PROGNOSIS AFTER ACUTE CORONARY ANGIOPLASTY THERAPY OF ACUTE MYOCARDIAL INFARCTION. Nathan Kander, M.D., William W. O'Neill, M.D., Eric Topol, M.D., Joseph A. Walton, Jr., M.D., Patrick D. Bourdillon, M.D., Eric Bates, M.D., F.A.C.C., Theresa Kryski, R.N., Bertram Pitt, M.D., F.A.C.C. University of Michigan, Ann Arbor, Michigan.

The prognosis of patients undergoing acute coronary angioplasty (PTCA) during acute myocardial infarction (AMI) is undefined. We have performed acute PTCA on 80 consecutive patients, presenting within 12 hours of symptom onset from December, 1983 to March, 1985. All patients have been followed for at least 6 months to assess survival, functional class, reinfarction and clinical restenosis rate.

While the overall 6 month survival was 86%, it was 93% for patients with successful reperfusion (rep) but only 45% for unsuccessful rep ($p < .001$). By univariate analysis, significant differences were present between survivors (S), and non-survivors (NS) These include age (S=52.9±10.5 yrs vs. NS=64.4±10.1, $p < .001$), anterior location of MI (S=Anterior 70% vs. NS=Anterior 100%, $p < .001$), Killip Class (S=1.64±.71 vs. NS=3.45±.68, $p < .001$), symptom duration (S=5.42±2.16 hrs vs. NS=7.25±2.0 hrs, $p < .05$), baseline ejection fraction (EF) (S 52.9±11.6 vs. NS 30.6±11.1, $p < .001$), and MI size (peak CPK S=2993±2329 vs. NS=8505±5379, $p < .001$) All mortality occurred during initial admission. Of patients with successful rep, 81% have NYHA Class O or I angina, 8% have had clinical reinfarction and 8% have clinical restenosis.

We conclude that (1) successful acute PTCA during AMI may improve 6 month survival; (2) a low incidence of restenosis or reinfarction exists; (3) Prognosis is adversely affected by age, initial extent of jeopardized myocardium, duration of ischemia, final size of infarction and reperfusion status.

TRANSLUMINAL CORONARY ANGIOPLASTY IN THE ACUTE INFARCT-RELATED ARTERY. SHORT AND LONG TERM RESULTS.

Siguemituzo Arie, M.D., Giovanni Bellotti, M. D., Hedy Checchi, M. D., Lelio Alves, M. D , José A. F. Ramires, M. D., and Fulvio Pileggi, M. D., F. A. C. C. - Heart Institute, University of São Paulo, Brasil.

Between october 1981 and april 1984, 56 patients (pts) with acute myocardial infarction (MI) were successfully submitted to transluminal coronary angioplasty (TCA). In 50 pts TCA was performed after pharmacological (43 pts) or mechanical (7 pts) recanalization of the occluded artery and in 6 pts after evidence of severe obstruction of the infarct-vessel. Angiographic study repeated 1 - 2 weeks later in 48 pts showed a decrease in the degree of obstruction from 92 ± 6 to 16 ± 10% and an improvement of LVEF from 0.55 ± 0.16 to 0.59 ± 0.17 ($p < 0.05$). Early coronary re-occlusion occurred in 3 (5%) pts, 2 (4%) pts died after surgical treatment for severe mitral regurgitation and 1 died of cerebral hemorrhage due to streptokinase administration.

Late clinical course (16 - 42, mean 26 months) was avaliable in 50 pts. Re-occlusion of the treated vessel in 5 (10%) pts and severe re-estenosis in 4 (8%) were observed One pts died suddenly Thirty-six pts are assymptomatic. Late routine angiography (6-12 months) was performed in 23 of these 36 pts. No significant changes in the degree of residual obstruction and an additional improvement in the LVEF, mainly in pts with LVEF $\leq$ 0.50 (from 0.43 ± 0.05 to 0.60 ± 0.12, $p < 0.02$) were observed.

This study confirm that TCA can be performed in selected patients with acute MI with an acceptable complication rate. In most patients TCA is effective both to improve early and late ventricular function and to determine uneventful clinical course.

EARLY POSTINFARCTION UNSTABLE ANGINA: RESULTS OF CORONARY ANGIOPLASTY.

Pim de Feyter, MD, Patrick W Serruys MD, Marcel vd Brand, MD, Paul G Hugenholtz, MD, FACC.
Thoraxcenter, Rotterdam, the Netherlands.

Surgeons are generally reluctant to perform bypass surgery in the setting of a recent myocardial infarction. Coronary angioplasty (CA), as an alternative to bypass surgery, in pts with early postinfarction unstable angina (PUA) might be effective to relieve ischemic symptoms and to prevent re-infarction. PUA was defined as chest pain at rest, associated with ST-T changes. CA was performed in all 44 pts with early PUA within 30 days (mean 12±8) after preceding MI. Thirty seven (84%) were males; the mean age 59.3 (range 36-73 yrs). Multivessel disease was present in 39%. Thirty six pts were refractory to pharmacological treatment consisting of a combination of intravenous nitroglycerine, bêta-blockers and Ca-antagonists. Eight pts were initially stabilised, but symptomatic with light exertion. The preceding MI was of small or moderate size in the majority of the pts. All pts were followed for at least 6 months.
Results: The initial CA successrate was 89% (39/44 pts). There was no death related to CA; a MI complicated CA in 9% (4 pts) and urgent bypass surgery was necessary in 7% (3 pts). At 6 months follow up recurrence of angina occurred in 26% (10/39 pts). The angiographic restenosis rate was 33% (11/33 pts); 6 pts refused repeat angiography).
This study suggests that in selected pts CA for unstable angina within 30 days after preceding MI of small or moderate size can be accomplished with an acceptable risk, a high initially success rate, and sustained beneficial effect in the majority of the patients.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #260/261
Newer Technologies to Assess Anatomic and Functional Coronary Artery Disease

INTRAOPERATIVE EVALUATION OF THE EFFECTS OF CORONARY REVASCULARIZATION BY COLOR FLOW MAPPING 2-D DOPPLER ECHOCARDIOGRAPHY AND THERMOCARDIOGRAPHY

Shunei Kyo, Hideo Adachi, Shinichi Takamoto, Makoto Matsumura, Yuji Yokote, Ryozo Omoto. Saitama Medical School, Saitama, Japan

To evaluate the effects of coronary revascularization (CR), we examined 11 patients intraoperatively by high resolution color flow mapping 2-D Doppler Echocardiography (HR-2DD, 5MHz & 7.5MHz) and real-time Thermocardiography (TC). In HR-2DD minimum detectable velocity is 2 cm/sec, and in TC an ischemic myocardium is displayed as a relative cold area with a thermal dissolution power of 0.1°C. The average bypass flow (BF) of 21 saphenous vein grafts (SVG) was 74 ±30 ml/min measured by electro-magnetic flow meter (EMFM), and HR-2DD could semi-quantitatively visualized BF in 19 SVG (91%) except two SVG which blood flow was less than 20 ml/min measured by EMFM. Also HR-2DD demonstrated no stenosis nor turbulent flow pattern at the anastomosis. TC could visualize BF in all 21 SVG and 6 left internal mammalian arterial grafts (LIMAG), however, EMFM and HR-2DD failed to detect BF in 2 LIMAG respectively. In four patients pre-operative TC demonstrated an ischemic area in LV anterior wall where a homogeneous myocardial blood perfusion was confirmed to be restored by postoperative TC. It was compatible to the pre- and post-operative thallium scintigram. In conclusion, a combined use of HR-2DD and TC is useful in immediate intraoperative confirmation of smooth bypass blood flow through the anastomosed grafts and evaluation of the restored myocardial blood perfusion in the critically ischemic myocardium after CR.

RAPID IDENTIFICATION OF ISCHEMIC MYOCARDIUM BEFORE AND AFTER BYPASS SURGERY BY COMBINED USE OF INTRAOPERATIVE 2-DIMENSIONAL ECHOCARDIOGRAPHY AND ATRIAL PACING. Martin E Goldman MD FACC, Bruce P Mindich MD FACC, Theresa Guarino RN, Joseph A Gomes MD FACC, Singhoi Chow MD, Arthur Schwartzbard, Valentin Fuster MD FACC, Mt. Sinai & St. Lukes Hosp, NY

Angiographic coronary anatomy does not necessarily identify myocardial regions at greatest ischemic risk in patients with multi-vessel coronary disease. Once jeopardized myocardium is defined, ischemic complications during coronary bypass surgery(CABG) may be reduced by preferential graft sequence and/or selective cardioplegic infusion. Therefore, we performed direct on heart 2-D echocardiography (2-DE) in the LV short axis plane during incremental atrial pacing (AP) (80-120 bpm) pre- & post CABG in 15 patients (pts) with multivessel disease. 2-DE images were analyzed blindly for regional wall contractility, & ejection fraction (EF) at each AP rate. Cardioplegic infusion, which by 2-DE is similar to a perfusion scan, was also imaged.

Although EF remained constant during AP pre-CABG, 11/15 pts developed new contractility abnormalities (abn) in 18/60 analyzed segments(most commonly in the anteroseptal region). However, the ischemic region could not be predicted from the coronary anatomy due to severe multivessel disease. Regions with cardioplegic perfusion defects by 2-DE correlated with areas of AP-induced contractility abn. During AP post-CABG, contractility ↑ in 11/15 pts and 14/18 regions originally abn during pre-CABG AP, while global EF ↑ in only 3/15 pts.

Therefore, intraoperative 2-DE during AP identifies ischemic zones that correlate with severe coronary obstructions, but cannot be predicted solely by angiographic criteria. Abnormal cardioplegic perfusion of myocardial regions also identified ischemic zones. Detection of segments at high ischemic risk by intraoperative 2-DE & AP may guide selective cardioplegia or CABG sequence; relief of ischemia can be confirmed post-CABG by improved regional (but not global) wall motion.

CURVATURE ANALYSIS: A NEW, ASSUMPTION-FREE METHOD FOR QUANTITATION OF REGIONAL VENTRICULAR FUNCTION. G.B. John Mancini, M.D., F.A.C.C., Scott F. DeBoe, B.S., Michael T. LeFree, B.S., Edward Anselmo, B.S., Robert A. Vogel, M.D., F.A.C.C., VAMC and University of Michigan, Ann Arbor, MI

Traditional assessment of regional wall motion abnormalities (WMA) entails assumptions regarding coordinate, reference and indexing systems and the uniformity of left ventricular contraction. Detection of shape characteristics is proposed as an alternative approach to measurement of ventricular function that is independent of these assumptions. Curvature (C), a numerical shape parameter, is given by the reciprocal of the radius of a circle that best fits a curve at a given point. Regional C of 30° RAO left ventriculograms was quantitated with a commercial image processing unit in 20 normal (N) patients and 48 with WMA. End-diastolic shape quantitation showed only small differences between N and WMA groups, but end-systolic (ES) C showed marked regional abnormalities in groups with isolated anterior (ANT) or inferior (INF) hypokinesis or both.

	Wall Motion Groups			
ES C	N(n=20)	ANT(n=20)	INF(n=15)	ANT+INF(n=13)
ANT	195±92	305±106*	224±112	292±91*
INF	35±140	7±121	209±166*	139±150*

(C reported in normalized, dimensionless units, mean ± SD, *p<.05 vs. N) The increased values for C noted in the areas of WMA are in keeping with a more globular regional shape compared to N. Thus, end-systolic C analysis allowed detection of regional shape abnormalities that reflected underlying dysfunction. C analysis provides a conceptually different approach to the assessment of regional ventricular dysfunction that is independent of the usual assumptions mandated by traditional methods.

MEASUREMENT OF CORONARY BLOOD FLOW AND REGIONAL MYOCARDIAL PERFUSION USING HYDROGEN DILUTION AND WASHOUT SUBSELECTIVE CATHETER TECHNIQUES. Harold Z. Friedman, M.D., Glenn J. Beauman, M.S., Mark J. McGillem, B.S., G.B. John Mancini, M.D., F.A.C.C. and Robert A. Vogel, M.D., F.A.C.C., V.A. Medical Center, University of Michigan, Ann Arbor, Michigan

The measurement of coronary blood flow and myocardial perfusion are both clinically difficult and important. We have developed two new techniques for the assessment of these parameters. Absolute coronary blood flow (CBF) is measured using a 2 French platinum electrode-tipped, intracoronary catheter. A 25% hydrogen saturated reference solution is infused through two side-holes located 5 cm from the catheter tip. Using steady-state dilutional analysis, CBF is calculated using comparison of the electrode potentials during 10 s reference solution infusions (15 ml/min) under coronary occluded and non-occluded conditions. The second technique measures regional myocardial perfusion (RMP) using subselective intracoronary infusion of 10 ml hydrogen saturated saline over 30 s. During steady-state conditions, RMP is calculated by inert gas washout analysis of the electrode potential of a platinum-tipped catheter located in the pulmonary artery. Using an open-chest canine preparation, validation of these techniques was accomplished using electromagnetic flowmeter determined blood flow varied (0-300 ml/min) by dobutamine, papaverine, atrial pacing, and coronary ligation. CBF and RMP were found to correlate closely with absolute (r=0.96) and relative (r=0.94) blood flow, respectively. These data suggest that CBF and RMP can be measured accurately using an inexpensive, inert tracer and subselective coronary catheterization.

HUMAN EXPERIENCE WITH SYNCHRONIZED CORONARY SINUS RETROPERFUSION (SCSR): FEASIBILITY AND SAFETY - Joel M. Gore, MD, Bonnie H. Weiner, MD, Kathy M. Sloan, RN, Joseph R. Benotti, MD, Okike N. Okike, MD, Thomas J. VanderSalm, MD, Steven P. Ball, RN, Jeanne Corrao, RN, Joseph S. Alpert, MD, James E. Dalen, MD, UMass Medical School, Worcester, MA

Animal studies have demonstrated the value and safety of SCSR in models of acute unstable ischemic heart disease. Accordingly, we have initiated a Phase I trial to evaluate the feasibility and safety of this intervention. To date, 5 pts with acute anterior wall ischemia refractory to maximal medical therapy have been evaluated. SCSR was initiated at the bedside by inserting 8F catheters (C) into the femoral artery and coronary sinus for collecting and delivering oxygenated blood to the myocardium. An autoinflatable balloon at the CS catheter tip effects temporary coronary sinus occlusion. This permits pulsatile retrograde delivery of arterial blood to the myocardium ECG synchronized with diastole. With institution of SCSR, ECG changes of anterior ischemia improved in 3 out of 5 pts with no hemolysis or fall in platelet counts. Comparison of preselected parameters during the 36 hours prior to SCSR and on SCSR revealed:

	Pre SCSR	On SCSR	p
IV Nitro	.786 mg/min/hr	.731 mg/min/hr	NS
Morphine	.74 mg/hr	.17 mg/hr	p<.02
#Angina Episodes	.71 epis/hr	.008 epis/hr	p<.05
SL Nitro	.23 tab/hr	0 tab/hr	p<.05

SCSR has been maintained for up to 3 days with clinical benefit and without adverse effects. Direct inspection of the CS in 4 pts at the time of coronary bypass surgery revealed no traumatic injury. Conclusion: SCSR is a feasible and safe intervention capable of alleviating myocardial ischemia in pts with unstable, ischemic heart disease.

ANATOMIC AND FUNCTIONAL ASSESSMENT OF CIRCUMFLEX CORONARY ARTERY STENOSES USING VIDEODENSITOMETRY.
Maryl R. Johnson, M.D., F.A.C.C., Steven R. Fleagle, B.S., Robert F. Wilson, M.D., Carl W. White, M.D., F.A.C.C., Loren F. Hiratzka, M.D., Melvin L. Marcus, M.D., F.A.C.C., Steve M. Collins, Ph.D., David J. Skorton, M.D., F.A.C.C., University of Iowa, Iowa City, IA

We have shown that videodensitometric analysis (VID) of left anterior descending (LAD) and right coronary artery (RCA) stenoses (S) allows accurate and reproducible estimation of S lumen size, as defined by quantitative coronary angiography (QCA), and functional significance, as defined by intraoperative Doppler reactive hyperemia studies. Due to the posterior location of the circumflex (Cx), however, intraoperative studies cannot be performed on Cx S. We recently validated the use of an intracoronary Doppler catheter for determining coronary flow reserve in the catheterization laboratory by measuring the peak-to-resting velocity ratio (PRVR) following maximal dilation with intracoronary papaverine. Therefore, in this study we assessed the ability of VID to assess the anatomy and physiology of Cx S. Cine frames of Cx S from 8 patients were digitized. Following background subtraction, integrated optical density (IOD), an index of lumen area, was computed. IOD was compared to minimal lumen area defined by QCA and to PRVR measured using the intracoronary Doppler catheter. Shown below are results from this study and from our studies of the VID of LAD and RCA S.

	Cx (n=8)	LAD (n=17)	RCA (n=19)
IOD vs. QCA	r = 0.78	r = 0.83	r = 0.72
IOD vs. PRVR	r = 0.77	r = 0.77	r = 0.79

CONCLUSIONS: VID provides accurate estimation of Cx lesion lumen size and functional significance. Therefore, we can now conclude that VID allows accurate assessment of stenoses in all three coronary arteries.

INCIDENCE AND MANAGEMENT OF LIMB ISCHEMIA DURING THE USE OF CURRENT WIRE-GUIDED INTRA-AORTIC BALLOON PUMPS
James D. Alderman, M.D., Gregory I. I. Gabliani, M.D., Cynthia C. Brewer, R.N., M.S., Beverly H. Lorell, M.D., F.A.C.C., Richard C. Pasternak, M.D., F.A.C.C., Donald S. Baim, M.D., F.A.C.C. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA.

We followed 78 patients (pts) who had percutaneous, wire-guided intra-aortic balloon pumps (IABP) between 8/83 and 7/85, including 53 men and 25 women with a mean age of 63, using clinical exam and ankle-brachial index. Indications for IABP were unstable angina (58 pts), cardiogenic shock (17 pts), left main disease (10 pts), instability during catheterization (3 pts), electively pre-bypass surgery (5 pts), other (7 pts). The mean duration of IABP counterpulsation was 3.4 days.

Post-insertion limb ischemia was noted in 37 pts (47%) - 24/53 men (45%) and 13/24 women (54%). IABP removal alone led to resolution of ischemia in 24 pts (65%), while the remaining 13 pts (35%) required operative intervention. Only 4 had longterm sequelae (one each: compartment syndrome, femoral-popliteal bypass, gangrene, death during embolectomy). Of the 41 pts without clinical limb ischemia during IABP, only 3 developed a vascular complication (hematoma), one of whom required surgery. Of the 12 pts who had previously known peripheral vascular disease (PVD), 8 (75%) developed ischemia during IABP versus 29/66 (44%) pts without PVD. Pts with limb ischemia and PVD were more likely (4/8=50%) to require surgical intervention than pts with limb ischemia without PVD (9/29=31%). Moreover, the incidence of longterm sequelae post-operatively was higher in PVD pts (2/4=50%) than non-PVD pts (2/9=22%). There was no difference in the incidence of limb ischemia using 10.5 French(F) IABP (16/31=52%) versus 12F IABP (18/41=44%). There were 10 in-hospital deaths, but only 1 death was IABP-related (general anesthesia complication during vascular repair).

Thus, despite advances in IABP technology: 1)Limb ischemia remains a frequent (47%) complication of IABP therapy, particularly in pts with PVD, 2)While limb ischemia resolves in most pts when the IABP is removed, approximately 17% of all pts who undergo IABP will require vascular surgery, 3)50% of pts with known PVD who develop ischemia require surgery, 4)IABP complications only infrequently lead to longterm sequelae or death.

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #260/261
Technologic Innovations in Coronary Artery Disease Assessment

VISUALIZATION OF INTERNAL MAMMARY ARTERY BYPASS GRAFT BY DIGITAL INTRAVENOUS ANGIOGRAPHY. EXPERIENCE WITH 42 CONSECUTIVE PATIENTS.
Gerard M. Guiraudon, M.D., F.A.C.C., Richard N. Rankin, M.D., William J. Kostuk, M.D., F.A.C.C., George Jablonsky, M.D., F.A.C.C., James E. Brown, M.D., John Rowsom, M.D., University Hospital, London, Ontario, Canada.

The internal mammary artery (IMA) has been established as the best conduit for coronary artery bypass graft (CABG). Digital intravenous angiograph (DIVA) was obtained in 42 consecutive patients (pts) six weeks after surgery, to visualize the IMA graft and to establish the value of the DIVA as a non-invasive test for follow-up.

There were 42 left IMA grafts and 2 right IMA grafts. Thirty two angiograms were obtained for control. The technical quality of DIVA was excellent (5pts), good (34pts) and poor (5pts). The IMA was visualized to the heart border (6), the lower aortic arch (26), the upper aortic arch (7), above the aortic arch (3) and not visualized (2). The degree of visualization depended on the technical quality of the DIVA. Excellent DIVA showed IMA graft to the heart border (5/6), and good DIVA showed IMA graft to lower aortic arch (24/34). Seven CABG were incidentally seen on good and excellent DIVA. Of the 2 IMA grafts not visualized one was found patent, but of small caliber on the angiogram.

We conclude that the IMA graft has an excellent patency rate (98%) and that DIVA is an excellent test for IMA graft visualization (100% specificity, 98% sensitivity).

DELINEATION OF MYOCARDIAL ISCHEMIA IN PATIENTS BY POSITRON EMISSION TOMOGRAPHY WITH $H_2{}^{15}O$
Edward M. Geltman, M.D., F.A.C.C., James J. Spadaro, Jr., M.D., Keith A.A. Fox, M.B., Ch.B., Ali A. Ehsani, M.D., F.A.C.C., and Burton E. Sobel, M.D., F.A.C.C., Washington University School of Medicine, St. Louis, MO

We have previously quantified myocardial perfusion in dogs by positron tomography with oxygen-15 labeled water ($H_2{}^{15}O$) and subtraction of blood pool radioactivity. To determine whether ischemia can be delineated in patients, we performed positron emission tomography in 37 patients (12 controls and 25 with angiographically documented coronary artery disease) after i.v. infusion of 50-150 mCi of $H_2{}^{15}O$ and inhalation of 50-75 mCi of $C^{15}O$ (for calculation of blood pool $H_2{}^{15}O$ radioactivity) at rest (n = 13) or sequentially at rest and after vasodilator stress (n = 25) induced with dipyridamole (.56 mg/kg i.v.). In controls, myocardial perfusion appeared to be quite homogeneous both at rest and with stress (average relative to maximal regional perfusion at rest: septum = .80; anterior wall = .88; lateral wall = .93; posteriolateral wall = .90; and with stress: .87, .88, .95, and .87, respectively). In 75% of patients with prior infarction marked inhomogeneities of flow were evident at rest or with stress (relative flow in peri-infarct zones averaging .39 of that in normal zones at rest and .55 with stress). In patients with coronary stenosis without infarction, inhomogeneities were seen in 20% at rest and 80% with stress (ischemic zone relative flows = .79 at rest and .57 with stress). Thus, positron tomography with $H_2{}^{15}O$ and blood pool subtraction permits noninvasive delineation of myocardial ischemia in patients.

EXPERIENCE WITH USE OF THE REPERFUSION CATHETER PRIOR TO EMERGENCY BYPASS SURGERY. Tomoaki Hinohara, MD, John B. Simpson, MD, Harry R. Phillips, MD, Eric B. Carlson, MD, William O'Callaghan, MD, and Richard S. Stack, MD, Duke University Medical Center, Durham, NC

Refractory coronary artery occlusion during PTCA may result in myocardial infarction (MI) or death despite emergency revascularization with coronary artery bypass surgery (CABG) unless immediate reperfusion can be established. A recently developed 4.3 FR coronary infusion catheter with multiple sideholes or "reperfusion catheter" (RPC), was utilized to re-establish blood flow prior to emergency CABG.

In the past seven months, since the introduction of the RPC, 19 out of 337 PTCA patients (pts) (5.6%) underwent immediate CABG due to unsuccessful PTCA at our institution. Insertion of the RPC was attempted in 14 pts (13 pts. with total and one pt with near total occlusion). Total occlusions following initial PTCA were associated with chest pain and ST segment elevation and were refractory to multiple repeat balloon dilatations and vasodilators. The RPC was successfully placed across the coronary artery obstruction in 13 pts (93%). In all pts with successful RPC placement, angiographically documented reperfusion was re-established associated with relief of chest pain. 2 pts had persistent ST segment elevation (1 pt with pre-PTCA MI and 1 pt with intracoronary thrombosis). There were no deaths. All pts underwent immediate CABG with the RPC in place and tolerated the procedure well.

Immediate reperfusion following refractory coronary occlusion during PTCA may be achieved using the RPC prior to CABG. This procedure significantly reduces the morbidity and could potentially reduce the mortality associated with coronary occlusion during PTCA.

ANGIOSCOPY FOR GUIDANCE OF LASER RECANALIZATION IN MAN. George S. Abela, M.D., James M. Seeger M.D., Enrico Barbieri, M.D., Carl J. Pepine, M.D., F.A.C.C., C. Richard Conti, M.D., F.A.C.C., University of Florida and VAMC, Gainesville, FL.

Seven patients (ages 52-75) had angioscopy of the peripheral circulation during surgery. All patients had total occlusion of the superficial femoral artery at angiography and were undergoing bypass surgery for symptomatic occlusive arterial disease. Three angioscopes were used: a 1.7 mm Optiscope; a 2.8 mm Laser Optiscope (Trimedyne, Inc.) and a 3.2 mm BF Scope (Olympus Corp.). Visualization inside the vessel was done by introducing the scopes through an arterial cut-down with continuous saline infusion. The scopes were adapted to a video camera and images displayed on a monitor. Lasing was done from an Argon laser using a 300 μm core fiber and a 2 mm metal tip. Energy was varied using incremental rises, first in power (1-8 watts), then in exposure (1-10 sec) until recanalization occurred.

Results: Angioscopy showed total atherosclerotic occlusion of 6 superficial femoral arteries and fresh thrombus in 2 arteries and 1 graft. Using the angioscope, the optical fiber was positioned at the center of the arterial occlusion and recanalization done under direct visualization. Adequate visualization was acheived by all 3 scopes. Passing the 1.7 mm scope through the recanalized artery showed charring along the arterial walls. Intimal flaps were seen in 2 arteries. Communication with the artery distal to the occlusion was confirmed by appearance of blood. The length of recanalized segments was 5 ± 1.4 cm. Two of nine vessels perforated at an average of 4.8 cm from the point of fiber entry into the plaque.

Conclusions: Angioscopy maybe useful in averting perforation during laser recanalization and could also be used as a diagnostic device.

DEFINITION OF NEW PATHOPHYSIOLOGIC MECHANISMS AND ALTERED DECISIONS: AN OUTCOME OF INTRAVASCULAR ANGIOSCOPY Warren S. Grundfest, M.D., Frank Litvack, M.D., Todd Sherman,M.D., Myles E. Lee, M.D., Robert Carroll, M.D., Aurelio Chaux, M.D., Robert Kass, M.D., Jack Matloff, M.D., FACC, James S. Forrester, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, CA.

Intraoperative angioscopy provides images of the endothelial surface with <0.2 mm spatial resolution. The angioscopes have an outer diameter of 1.3-2.8 mm, allowing entry into small peripheral vessels, prosthetic grafts, and branches of coronary arteries. In 59 operations (33 coronary, 26 peripheral) there were 131 examinations (86 arteries, 30 new anastomoses, 10 old grafts, 5 argon laser femoral artery angioplasties and 5 in-situ vein grafts). A clear viewing field was created by infusion of pressurized saline in peripheral vessels and crystalloid cardioplegia in arrested hearts.

In 30% of the cases, angioscopy revealed clinically important but unsuspected anatomic details. Information that altered surgery included 2 misplaced anastomotic sutures, 2 partially obstructive intimal flaps requiring revision, 2 atheroma at planned graft sites which altered their placement, and 3 residual thrombi after allegedly complete balloon thrombectomy. Critical coronary detail included detection of 5 angiographically undetected thrombi in unstable rest angina. In addition, the spectrum of acute intravascular abnormalities was substantially greater than that described at routine postmortem: we found strands of sessile thrombi in progressive angina, and tiny hemorrhagic ulcers on both otherwise normal endothelium and on atheromatous plaques (all undetectable on review of coronary angiograms). We conclude that angioscopy can alter surgical procedures, and provides unique information about pathophysiologic mechanisms in coronary syndromes which can be obtained by no other existing technology.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #360/361
Cardiac Studies With Computed Tomography and Digital Angiography

TEMPORAL FOURIER TRANSFORM OF DIGITAL ANGIOGRAMS FOR LEFT VENTRICULAR REGIONAL WALL MOTION ANALYSIS
Kazuhiro Katayama, M.D., Thomas F. Widmann, M.D., Brian Guth, Ph.D., Jong Dae Lee, M.D., Rainald Seitelberger, M.D., Gerd Heusch, M.D., Mark Miller, B.S.E.E. and Kirk L. Peterson, M.D., F.A.C.C.
University of California, San Diego, California

To determine whether the first harmonic of a temporal Fourier transform(TFT), applied pixel-by-pixel on time-intensity curves, can detect subtle wall motion abnormalities due to ischemia, 6 dogs were instrumented with a LV micromanometer, circumflex hydraulic cuff occluder, and sonomicrometers on the inferior (ischemic) and anterior (non-ischemic) walls. LV images obtained after contrast injection via pulmonary artery were compared with dimension signals in control(C) and three progressive levels of stenosis (StI, StII, StIII). Normalized, digital functional images (512x512 matrix, 256 shades of gray/pixel) were divided into anterior, apical, and inferior areas to acquire regional mean phase(PH, degrees) and amplitude (AMP, intensity units) values. Results (mean±SEM):

	Non-Ischemic			Ischemic		
	%WTh	PH	AMP	%WTh	PH	AMP
C	34±6	148±6	143±7	22±2	194±6	164±7
StI	38±6	148±6	153±5*	17±2*	207±6*	158±6
StII	39±7	146±6	157±7†	8±2†	217±7†	143±8†
StIII	41±7	147±11	167±6†	1±2†	233±9†	125±6†

[%WTh: wall thickening(%), *=p<0.05, †=p<0.01]

There was a progressive increase in PH and decrease in AMP in ischemic areas as %WTh fell (PH vs. %WTh:r=-0.61, p< 0.002; AMP vs. %WTh:r=0.77, p<0.001). Heart rate and peak left ventricular pressure showed no significant changes during stenoses. We conclude that quantitative functional images, generated from a temporal Fourier transform, are sensitive for the detection of LV regional wall motion abnormalities during mild to severe degrees of ischemia.

QUANTITATION OF AORTIC REGURGITATION BY COMPUTER ANALYSIS OF DIGITAL SUBTRACTION ANGIOGRAPHY

Paul A Grayburn MD, Steven E Nissen MD, Jonathan L Elion MD, Joyce Evans, and Anthony N DeMaria MD, FACC. University of Kentucky and VA Medical Center, Lexington, Ky.

Currently existing methods for the quantitation of aortic regurgitation (AR) are cumbersome and limited in accuracy, particularly in the presence of mitral regurgitation. Recently, the development of digital subtraction angiography (DSA) has provided a potential method for the quantitative assessment of AR by analysis of time-density curves from radiographic contrast in the aorta and left ventricle (LV) following aortography. Therefore, we developed and validated a method for determining regurgitant fraction (RF) by DSA in an animal model of AR. Following thoracotomy, an appropriately sized electromagnetic flow probe (EMF) was positioned on the ascending aorta to measure forward and regurgitant flow. AR was produced by manipulation into the aortic valve orifice of a custom-designed non-metallic basket catheter capable of inducing varying degrees of AR. A total of 16 individual regurgitant lesions were produced in 5 mongrel dogs. For each level of AR, a DSA aortogram was performed with 6 ml of contrast /second for 3 seconds utilizing ECG gated pulse-mode X-ray, an R-wave triggered contrast injection, and mask-mode subtraction of the 512 x 512 pixel image. Logarithmic transformation was utilized to ensure a linear relationship between contrast concentration and image intensity. A rectangular region of interest (175 x 20 pixels) was positioned in the ascending aorta and LV outflow tract, and integrals of time-intensity curves were generated for both. Regurgitant fraction was computed as the ratio of LV to aortic summated intensity. RF by EMF was calculated as the ratio of reverse to forward flow by planimetry of the EMF flow tracings and varied from 6.9% to 82.6%. The RF by DSA and EMF were compared by linear regression analysis; the correlation coefficient was r=0.82 for all dogs and r > 0.94 in individual animals. Thus, these data demonstrate that in an animal model of AR, DSA may be utilized to obtain time-density contrast curves of the LV and aorta from which regurgitant fraction may be calculated. Values of regurgitant fraction obtained by DSA show a good correlation to those measured by EMF.

ULTRAFAST COMPUTED TOMOGRAPHY DURING EXERCISE BICYCLE ERGOMETRY

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Twelve patients (pts) with documented coronary artery disease underwent ultrafast computed tomographic (CT) evaluation during bicycle ergometry to assess left ventricular (LV) function. There were 10 males and 2 females, ($\bar{X}$) age = 52. Eleven pts were on cardiac medications at the time of evaluation. Pts were exercised to fatigue or symptoms by a standard protocol in the semi-supine position, starting at 25 watt-seconds and augmenting workload every 2 minutes by 25 watt-seconds. Peak workload averaged 75 watt-seconds. Pts received several 25cc injections of contrast medium with a total dose $\bar{X}$ = 104cc. Initial studies were performed at rest and within 10-15 seconds of exercise termination. Pts were monitored by EKG throughout the exam. Seventeen scans/sec, covering 1 cardiac cycle were performed at 4 to 8cm levels of the LV at rest and immediately after exercise in each pt. Seven pts had normal ejection fraction (EF) responses to exercise increasing from 3%-19%, $\bar{X}$ = 10 ± 6.4%. Five pts had abnormal EF responses to exercise decreasing from 2%-13%, $\bar{X}$ = 8 ± 4.3%. Seven pts had normal end-diastolic dimension (EDD) responses to exercise either not changing or decreasing from 0-16%, $\bar{X}$ = 8.3 ± 5.4%. Five pts had abnormal EDD responses to exercise increasing from 6%-34%, $\bar{X}$ = 15 ± 14.3%. Nine pts had normal end-systolic dimension (ESD) responses to exercise decreasing from 2%-43%, $\bar{X}$ = 21 ± 15.1%. Three pts had abnormal ESD responses to exercise increasing from 13%-16%, $\bar{X}$ = 20 ± 6.5%. Ultrafast CT has the potential for measuring physiologic characteristics in pts with ischemic heart disease.

MEASUREMENT OF AORTIC REGURGITATION WITH CINE CT

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Current approaches to determining regurgitant volume provide qualitative or semi-quanitative information at best. We evaluated the ability of Cine CT (CCT) for precise quantitative assessment of regurgitant volume (RgV). CCT enables rapid imaging (17 frames per second) in cine mode that can be utilized to obtain accurate determination of nearly simultaneous right ventricular (RV) and left ventricular (LV) stroke volume (SV) (Simpson's rule reconstruction of serial short axis tomograms; end-diastolic minus end-systolic volume of each ventricle). Studies were performed during IV infusion of a non-ionic contrast agent, Iohexol. A chronically implanted proximal aortic electromagnetic flow probe (EMF) was utilized to measure LVSV and RgV. In 12 studies in the absence of induced aortic regurgitation the difference between nearly simultaneous RV and LV SV (range 11-34 ml) was minimal (mean 1.1 ml; range 0.1-3.2 ml). In 7 studies during induced aortic regurgitation (basket catheter through the aortic valve), the CT RgV (difference between LVSV and RVSV; range 4.0-10.5 ml) correlated closely with the EMF RgV (r=0.85, slope=1.05, y-intercept= -.08 ml, SEE=1.2 ml). Calculated regurgitant fraction (RgF) ranged from 13-38% of total forward SV. The mean difference between calculated CT RgF and EMF RgF was 3.6±2.6% (range 0 to 7%). Thus, precise quantitative measurements of RgV and RgF can be obtained with CCT. This technique should be directly applicable to the quantitative measurement of valvular regurgitation in patients.

NONINVASIVE EVALUATION OF AORTO-CORONARY BYPASS GRAFTS USING CINE-CT.

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Knowledge of the patency and flow characteristics of aorto-coronary bypass grafts is often essential for managing post-CABG pts, but is not presently attainable noninvasively. We evaluated 101 bypass grafts (30 pts; 2 wks to 11 yrs post-CABG) using rapid multi-slice cardiac Cine-CT. Eight gated 8 mm thick cross-sectional tomographic images from aortic arch to aortic valve were acquired at 10 consecutive electrocardiographic R waves, following peripheral IV injection of 30-45 ml of renografin-76. Scans were acquired at each level before, during, and after passage of the contrast bolus. Images were assessed qualitatively in cine format and semi-quantitatively by comparison of aortic root and bypass graft CT density-time curves. Patency for saphenous vein grafts (SVG) was defined as contrast-enhanced visualization at both the proximal aortic anastomosis and at one more caudal level. Of 85 SVG's, 64 were patent by these criteria; 58 had CT density-time curves that peaked with the aortic curve, and 8 had curves that peaked later suggesting reduced flow rate. Of 16 internal mammary grafts, 13 were patent by Cine-CT. Six pts (18 grafts) had selective graft angiography within 2 wks of Cine-CT. Cine-CT established the patency of 12 grafts, while invasive angiography only identified 11. Three patent grafts had CT density-time curves that peaked after the aortic curve, and these contained 50,60, and 75% stenoses. These data indicate that Cine-CT can accurately determine the patency and probable presence of disease in both saphenous vein and internal mammary bypass grafts, and in some cases may be superior to invasive angiography.

DETERMINATION OF CHANGES IN CORONARY BYPASS GRAFT FLOW RATE USING CINE-CT

John A. Rumberger, M.D., Ph.D., Andrew J. Feiring, M.D., Loren E. Hiratzka, M.D., Steven J. Reiter, M.D., William Stanford, M.D., and Melvin L. Marcus, M.D., F.A.C.C., University of Iowa and CV Center, Iowa City, Iowa

Assessment of coronary bypass graft (CBG) patency is highly accurate using computed tomography (CT). However, measurement of changes in CBG flow rate (necessary to assess graft function) have not been possible using conventional CT. We investigated the application of cine-CT (Imatron C-100, 50 msec scan acquisition) to measurement of relative CBG flow rates in anesthetized dogs following placement of a left innominate to left circumflex CBG (lateral saphenous vein). A broad range of CBG flow rates from maximum vasodilation (4:1 to 5:1 increase in flow over control, intra-CBG adenosine) to near zero (cuff occluder) were produced in each experiment. CBG flow velocity was continuously assessed using a cuff-type Doppler probe directly applied on the graft. During mechanical ventilation at each flow rate, twenty transverse tomograms were obtained at a level where both the ascending aorta and CBG were visualized. Scans were taken following bolus right atrial injection of a non-ionic contrast agent (Iohexol/Iopamidol, 15 cc over 2 sec). Simultaneous contrast clearance curves were constructed and characterized for the ascending aorta and CBG at each flow rate (n=38). A single, easily definable parameter, the time between the peak contrast opacification in the ascending aorta and the CBG, was found to inversely correlate with changes in CBG flow rates within each dog ($r=0.78$ to $r=0.94$, $p<.001$). Cine-CT way offer a minimally invasive means of determining CBG function (flow reserve) in addition to patency in man.

EXERCISE-INDUCED VENTRICULAR TACHYCARDIA: CATECHOLAMINE-SENSITIVITY VERSUS CYCLE-LENGTH-DEPENDENCY.

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To determine the triggering mechanism of exercise-induced ventricular tachycardia (VT), 24 patients (pts), ages ranging from 18 to 75 (mean 42.9) years, were studied. Eight pts manifested sustained and 16 pts nonsustained VT on 2 consecutive treadmill exercise testings (TET). None of them exhibited electrocardiographic evidence of myocardial ischemia prior to the onset of VT. Electrophysiologic studies (EPS) with pharmacologic testings were performed in all pts. Based on the mode of VT initiation, two groups (Gr) of pts were identified. In Gr I - 15 pts, VT could not be induced by programmed atrial and ventricular stimulation despite attainment of the ventricular cycle length at which VT was provoked by TET. The induction of VT subsequently required intravenous infusion of isoproterenol (2 - 8 μg/min) in these 15 pts. Intravenous propranolol (P) (0.2 mg/kg) but not verapamil (V) (0.15 mg/kg bolus followed by 0.005 mg/kg/min drip) prevented the inducibility of VT during intravenous isoproterenol infusion in all 15 pts. In Gr II - 9 pts, VT could be readily induced by atrial and ventricular stimulation while attaining a range of ventricular cycle lengths at which TET provoked the onset of VT. P could only slow the rate of VT but V suppressed VT inducibility in all 9 pts. We conclude that (1) the triggering mechanism of exercise-induced VT can be either primarily of catecholamine-sensitivity or of cycle-length-dependency and (2) the triggering mechanism so identified with EPS predicts responses to antiarrhythmic agents.

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #360/361
Ventricular Tachycardia—Mechanisms

ADENOSINE SENSITIVE VENTRICULAR TACHYCARDIA: EVIDENCE SUGGESTING CYCLIC AMP MEDIATED TRIGGERED ACTIVITY.

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Electrophysiologic studies were performed in three patients without structural heart disease who had exertionally related sustained ventricular tachycardia (VT). Programmed stimulation reproducibly initiated and terminated VT in all patients. Ventricular tachycardia was also initiated with isoproterenol infusion and showed cycle length-dependent characteristics, i.e., the cycle length of induced tachycardia was dependent on the preceding sinus or drive cycle length. The tachycardia was terminated by intravenous verapamil and by Valsalva and/or carotid sinus massage. β-adrenergic receptor blockade with propranolol prevented induction of VT either during programmed stimulation or catecholamine challenge. Adenosine, a nucleoside, whose only electrophysiologic effect on ventricular myocytes is antagonism of catecholamine-induced elevation of intracellular cyclic AMP also reproducibly terminated VT within a mean time of 8 seconds, range 4.5 to 15 seconds (IV dose 75 to 112.5 mg/kg).

Adenosine, verapamil, vagal maneuvers and β-adrenergic receptor blockade all decrease the slow inward calcium current either directly by modulating calcium channels or indirectly by inhibiting production of cellular cyclic AMP. These observations along with the characteristic response of the tachycardia to programmed stimulation and initiation of VT with catecholamines suggest that the ventricular tachycardia described in these patients may be due to cyclic AMP mediated triggered activity.

EPINEPHRINE INFUSION IN THE CONGENITAL LONG-QT SYNDROME

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The congenital long-QT syndrome (LQTS) is characterized by abnormalities of the T-U wave and a susceptability to ventricular arrhythmias (VA), especially in response to stress. To evaluate the role of catecholamines, 8 PTS with LQTS and 6 controls (C) with no clinical VA underwent infusion of graded doses of epinephrine (EPI). ECG was recorded continuously. Serum potassium (K+) sampled at each stage of the infusion in 3 LQTS and all C. 6/8 LQTS but 0/14 C had VA ($P = .0001$). Four LQTS had non-sustained ventricular tachycardia. The 8 LQTS had larger U-waves than C in the resting state (0.18 +/- 0.16 mV vs 0.07 +/- 0.03) and with each dose of EPI (0.2 +/- 0.17, 0.29 +/- 0.13, 0.41 +/- 0.25, 0.48 +/- 0.2 vs 0.13 +/- 0.05, 0.2 +/- 0.06, 0.19 +/- 0.03, 0.3 +/- 0.14). K+ fell from 3.97 +/- 0.47 MEQ/L to 2.65 +/- 0.92 in LQTS and 3.58 +/- 0.4 to 2.35 +/- 0.07 in C, not significantly different. CONCLUSIONS: (1) LQTS are more sensitive to EPI induced VA. This is coincident with more prominent U-waves (2) This sensitivity is not related to differences in K+; (3) The association of large U-waves and VA's suggest EPI induced afterdepolarizations as a mechanism for LQTS.

NON-UNIFORM RECOVERY OF EXCITABILITY IN THE LEFT VENTRICLE
Joseph A. Vassallo, MD, Dennis M. Cassidy, MD, Francis E. Marchlinski, MD, FACC, Alfred E. Buxton, MD, FACC, Mark E. Josephson, MD, FACC, University of Pennsylvania, Philadelphia, PA.

Dispersion of recovery of excitability in the LV was determined by catheter mapping and programmed stimulation in 17 patients (pts): Group 1 (8 pts; no ventricular tachycardia (VT) and normal QT), Group 2 (3 pts; long QT syndrome), and Group 3 (6 pts; sustained monomorphic VT, normal QT). Sinus rhythm activation mapping was performed and local refractory periods were determined at a mean of 11±3 LV sites per pt. Local refractory period was defined as the longest coupling interval of an extrastimulus which failed to elicit a response following an 8 beat drive from each LV site. Total recovery time at each LV site was defined as the local activation time plus local refractory period. Dispersion was defined as the widest range of refractory periods and total recovery time per pt. Normal dispersion of refractoriness and recovery time (Group 1) were 41±11 msec and 48±14 msec respectively. Group 2 had greater dispersion of refractoriness (93±23 msec) and recovery time (91±25 msec) than Group 1, $p<.005$. Dispersion of refractoriness was similar in Group 1 and Group 3 (48±20 msec) but recovery times were longer in Group 3 (72±22 msec) than Group 1, $p<.05$. We conclude: 1) Compared to normals, pts with long QT syndrome have greater dispersion of total LV recovery time which is predominantly due to a wide dispersion of local refractoriness. 2) Pts with VT and normal QT have a greater degree of dispersion of total recovery time than normal, however, this is due to dispersion of activation times rather than refractoriness. Thus, potentially arrhythmogenic nonuniform recovery of excitability in the LV may be due to dispersion of refractoriness or activation times depending upon the pathophysiologic substrate.

DEMONSTRATION OF THE PRESENCE OF SLOW CONDUCTION DURING SUSTAINED VENTRICULAR TACHYCARDIA.
Ken Okumura, M.D., Brian Olshansky, M.D., Richard W. Henthorn, M.D., F.A.C.C., Andrew E. Epstein, M.D., F.A.C.C., Vance J. Plumb, M.D., F.A.C.C., Albert L. Waldo, M.D., F.A.C.C. University of Alabama at Birmingham, Birmingham, Alabama.

To test the hypothesis that an area of slow conduction is present during reentrant ventricular tachycardia (VT), and that the earliest activation site during VT is within or orthodromically just distal to the area of slow conduction in the reentry loop , we studied 10 episodes of VT (mean rate 176±26 bpm) induced in 7 patients (pts) with ischemic heart disease. Rapid ventricular pacing (RVP) was performed at selected sites during VT, recording electrograms (EG) at the earliest activation site during VT (site A) and at a site close to the pacing site (site B). RVP from the RV apex during RBBB VT and from selected LV sites during LBBB VT (mean pacing rate 189±32 bpm) demonstrated constant ventricular fusion beats in the ECG except for the last captured beat (thus entrained VT) in 9/10. During entrainment, sites A and B were activated at the pacing rate and conduction time from the last pacing impulse to the last captured EG at site A (St-A interval) was 376±67 msec and spanned the diastolic interval, while that at site B (St-B interval) was only 24±10 msec. Also, during entrainment, site A had the same EG morphology as during VT, while site B had a different EG morphology, indicating that site A was activated in the same direction during entrainment as during VT. 8 episodes of VT were entrained at ≥ 2 different pacing rates and the St-A interval further increased during higher rate pacing in 4/8 while the St-B interval remained unchanged. RVP performed from the same site during sinus rhythm (mean pacing rate 195±40 bpm) showed an St-A interval of 109±41 msec ($p<0.001$ vs the value during entrainment) and an St-B interval of 28±13 msec. These data indicate that an area of slow conduction not demonstrable during sinus rhythm exists during VT, and that the earliest activation site during VT is at or just orthodromically distal to this area of slow conduction.

COMPARISON OF THE RESETTING RESPONSE TO SINGLE AND DOUBLE EXTRASTIMULI IN VENTRICULAR TACHYCARDIA: IMPLICATIONS FOR AN EXCITABLE GAP
Nicholas J. Stamato, M.D., Mark E. Rosenthal, M.D., Jesus M. Almendral, M.D., Mark E. Josephson, M.D., FACC Univ of Penn, Philadelphia, PA

Ventricular tachycardia (VT) may be reset by single ventricular extrastimuli (SVE). Three types of reset curves have been described-flat, flat + increasing, or increasing. The flat curve may result from reset in a circuit with a fully excitable gap. Since intervening tissue refractoriness may limit the ability of SVE to reset VT, we assessed the response to SVE and double ventricular extrastimuli (DVE) (the coupling interval of the first set to cause no resetting) in 56 VT. SVE reset 26 (46.4%) VT and DVE reset 43 (76.8%) VT. In 20 VT, response to SVE and DVE were compared to assess the role of intervening tissue refractoriness, SVE yielded flat responses in 10, flat + increasing in 5, and increasing in 5. DVE yielded flat responses in 7, flat + increasing in 6, and increasing in 7. The size of the gap (range of coupling intervals over which resetting occurred) was 55±34 ms with SVE and 92±41 ms with DVE, $p<0.001$. The length of the gap which was flat was 52±33 ms with SVE and 84±34 ms with DVE, $p<0.002$. In those VT reset by DVE as well as by SVE both the total reset gap (90±40 ms) and the flat portion of the reset gap (48±46 ms) was significantly longer than those reset only by DVE (50±37 ms) and (17±26 ms), $p<0.01$ and $p<0.03$ respectively. The cycle length of VT reset by DVE only (361±51 ms) was no different from those reset by both DVE and SVE (355±55 ms, p=NS). We conclude: 1) When SVE fail to reset a VT, DVE from the same site can reset VT; 2) Intervening tissue refractoriness plays a significant role in determining the reset response to SVE; 3) The resetting response to DVE reflects characteristics of the VT circuit; 4) SVE underestimate the size of the excitable gap.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #366/367
Antiarrhythmic Actions of Beta Blocking and Calcium Blocking Drugs

SUPRAVENTRICULAR TACHYCARDIAS (SVT) TREATED WITH CONTINUOUS PROPRANOLOL (P) INFUSIONS
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Because oral therapy is often contraindicated in hospitalized patients (pts), we assessed the efficacy of continuous propranolol (P) infusions in 9 intensive care unit pts with supraventricular tachycardia. Four pts had sinus tachycardia, 4 atrial fibrillation and 1 atrial flutter. The loading dose (LD) used depended upon the pts clinical response, higher dosages being used to control the more refractory arrhythmias (LD=52.2±38.3 µg/kg, SD). Using a volume of distribution (V_d) of 3.0 L/kg, the LD given, an elimination rate constant (K_d) of 0.23 hr^{-1} and standard pharmacokinetic formulas, the predicted plasma P concentrations (Cpred) and the initial maintenance dose (MD) were determined ($Cpred = LD/V_d \cdot K_g$; $MD = Cpred \cdot V_d \cdot K_d \cdot K_g$). The initial MD ranged between 6.1-56.0 µg/kg/hr (16.1±16.2 µg/kg/hr). Subsequent MD (3.9-74.9 µg/kg/hr) were determined by pt clinical response. The heart rate (HR) decreased from 146±22 to 98±16 ($p<0.0001$). A significant HR decrease was noted throughout the infusion. On a MD of 16.1±10.7 µg/kg/hr the P level measured (28±21 µg/L) did not differ significantly from the Cpred (22.8±16.8 µg/L). The duration of the infusion ranged between 16-288 hr (92±77 hr). A side effect-transient wheezing occurred in only 1 pt. This resolved by decreasing the infusion rate. We conclude that, by using the clinical response and simple pharmacokinetic formulas, continuous P infusions are safe and effective.

CLINICAL ELECTROPHYSIOLOGY OF FLESTOLOL, A NEW, POTENT, ULTRA-SHORT ACTING BETA BLOCKER.
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We studied the electrophysiologic effects of flestolol, a new ultra-short acting beta blocker, in 15 patients at 2 infusion rates: a 45 ug/kg bolus plus a 5 ug/kg/min infusion and a 60 ug/kg bolus plus a 10ug/kg/min infusion. The table shows intervals in msec after 15 min at each infusion rate (plasma levels 45±11 and 95±23 ng/ml):

	CONTROL	5 ug	10 ug	p*
Sinus cycle length	724±146	816±145	863±155	.0001
CSNRT	255±144	330±165	338±145	.02
AH	80±16	91±21	96±19	.0001
HV	46±10	46±10	47±10	NS
QRS	105±15	106±16	107±17	NS
QT_c	445±39	447±28	448±31	NS
$A\text{-}ERP_{600}$	216±42	216±49	212±47	NS
$AVN\text{-}ERP_{600}$	281±48	331±67	361±79	.0001
AVN Wenckebach cycle length	336±62	414±68	433±73	.0001
$V\text{-}ERP_{600}$	232±22	241±20	244±20	.03
$V\text{-}ERP_{400}$	216±17	225±19	226±18	.02
MAP (torr)	93±11	93±11	92±13	NS

CSNRT=corrected sinus recovery time; A=atrial; ERP_{600}=effective refractory period at cycle length 600 msec; AVN=atrioventricular node; V=ventricular; MAP=mean arterial pressure; *=linear trend significance.

At 5 mcg/kg/min, flestolol's electrophysiologic effects were comparable to those reported for 300 mcg/kg/min of esmolol, the first ultra-short acting beta blocker. A significant flestolol concentration-effect relationship ($p<.03$) was present for all variables which had significant dose-effect relationships. No toxicity occurred. In the post-infusion period, sinus cycle length decreased linearly with time (r=.99). At 30 min post-infusion, sinus and AVN Wenckebach cycle lengths had decreased to control values (716±136 and 342±53 msec) and flestolol plasma level to 4±2 ng/ml.

Conclusions: Flestolol had typical beta blocker effects on the sinus and AV nodes, increased V refractoriness, and did not alter A refractoriness or infranodal conduction. These doses of flestolol were safe in selected patients, had rapid onset and offset of action, and did not cause acute rebound.

EFFICACY OF ORAL DILTIAZEM TO CONTROL REST AND EXERCISE VENTRICULAR RESPONSE IN ATRIAL FIBRILLATION.
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In chronic atrial fibrillation (AF) resting ventricular response rate (VR) has been controlled using either digitalis (DIG), beta blockers, or more recently the calcium antagonist verapamil (V). During the increased sympathetic tone of exercise, however, VR is minimally affected with DIG alone but well controlled with addition of V. We evaluated the effect on exercise VR of DIG plus diltiazem (DIL), another widely used calcium blocker which unlike V does not increase DIG levels. Nine pts were studied, all exhibiting VR>100/min on 3 min exercise testing (0°, 3 MPH) while receiving "therapeutic" DIG (serum level 0.7 - 2.4 ng/ml). After baseline stress test pts received DIL 240 mg/day for one week and repeat studies performed. If exercise VR was >135/min (3 pts), DIL dose was increased to 360 mg/day with retesting one week later. Results (beats/min):

	DIG Alone	DIG + DIL	p Value
Rest VR	90.6 ± 15.7	72.3 ± 11.9	< .02
3 min Exercise VR	164.0 ± 28.2	119.3 ± 33.5	< .01

By adding DIL 8 of 9 pts (89%) achieved ≥15% VR reduction (mean 27 ± 15%) at peak exercise. There was no change in DIG levels during DIL therapy (1.4±0.5→1.4±0.6 ng/ml, pNS), and there were no episodes of symptomatic bradycardia. One week post DIL withdrawal VR had returned to baseline values.

Conclusion: The addition of DIL to DIG accomplished excellent exercise rate control in chronic AF with no effect on DIG level and no limiting adverse effects.

A COMPARISON OF ESMOLOL AND VERAPAMIL IN THE TREATMENT OF ATRIAL FIBRILLATION/FLUTTER.
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The effects of esmolol (E), an ultra short acting beta blocker and verapamil (V) were compared in controlling ventricular response (VR) in patients with atrial fibrillation/flutter in a randomized open label study. Patients with either recent onset (<48 hours, n=15) or old onset (≥48 hours, n=6) atrial fibrillation/flutter were randomized to receive E (n=11) or V (n=10). Baseline VR ranged from 116 to 172 bpm with a mean 146±6 ($\bar{x}$ ± SEM), for the V treated group and from 116 to 184 bpm (mean 143±5) for the E treated group. Demographics were similar for the two groups. E was given by continuous infusion in incremental doses from 2 to 16 mg/min for 10 minutes each following loading doses of 10 or 20 mg boluses. V was given in 5 or 10 mg I.v. boluses in two titration steps (if necessary). At the end of the titration, VR was reduced by 30% in the E group and 31% in the V group. Response was rapid in both groups. Nine of 11 (82%) achieved a VR of ≤ 100 bpm in the E group, compared with 5/10 (50%) in the V group. Conversions to normal sinus rhythm (NSR) occurred in 7/11 (65%) of the E group, and 3/10 (30%) of the V group. More pts with recent onset atrial fibrillation/flutter converted to NSR during titration (within one hour of onset of dosing) with E 6/7 (86%) as compared to V 2/8 (25%), ($p < 0.05$). Side effects included asymptomatic and symptomatic blood pressure reduction in 3/11 (27%) of the E treated pts and 6/10 (60%) of the V treated pts. E compares favorably with V in the acute therapy of atrial fibrillation/flutter.

VERAPAMIL FOR MULTIFOCAL ATRIAL TACHYCARDIA.
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Multifocal atrial tachycardia (MAT) may complicate the management of seriously ill patients (pts) and is often difficult to control. We treated 14 consecutive pts in MAT with verapamil (V) to assess its effect. All pts had serious, often pulmonary, illnesses; electrolytes and arterial gases were acceptable and none had contraindications to verapamil. Verapamil was given by slow IV push not exceeding 1 mg/min with constant heart rate (HR) and frequent cuff systolic blood pressure (SBP) measurement. Infusion was stopped for SBP less than 100, plateau in HR response, or conversion to sinus rhythm (SR). Oral (p.o.) verapamil 80 mg tid was given to 9 pts after IV trial at the attending staff's discretion. Four pts received 1 gm of calcium gluconate 5 minutes prior to treatment with verapamil (Group II); 10 pts did not (Group I).

The following results were obtained:

	Group I	Group II
V dosage (mg)	16.5	18.8
HR before V (bpm)	131 ± 16	119 ± 14
HR after V (bpm)	106 ± 18*	96 ± 13*
%Δ in HR	-19	-19
SBP before V (mmHg)	156 ± 20	125 ± 33
SBP after V (mmHg)	116 ± 25*	112 ± 36**
Δ SBP (mmHg)	40	13

*$p < .01$ vs before V; **$p < .05$ vs before V

Seven pts converted to SR, 6 remained in SR at 24 hr, 4 of whom were on p.o. drug.

SBP fell to less than 100 in 2 pts. No other complications occurred. Arterial gases were unchanged by V (n=7).

Thus, IV verapamil is safe and effective therapy for MAT, reliably lowering HR and often resulting in SR. Calcum appears to minimize drug-related hypotension without preventing antiarrhythmic efficacy.

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EFFECT OF CALCIUM CHANNEL BLOCKERS ON HEMODYNAMIC RESPONSES TO DEFIBRILLATION. Pamela Hite BS, Erwin Schröder MD, Robert Kieso MS, Michelle Hunt BS, Birgit Grimlund, Richard Kerber MD, FACC, U of Iowa, Iowa City, Ia

The hemodynamic response to sequences of ventricular fibrillation (VF)-defibrillation includes an adrenergic component, which is important for maintenance of blood pressure (BP) after successful defibrillation. Since calcium channel blockers (CCB) have antiadrenergic effects, we hypothesized that CCB might blunt the adrenergic response to defibrillation. VF was induced in 25 closed-chest dogs; each was externally shocked at least 4 times at 3 energy levels: 25 joules (J), 50J, and 100J to determine % defibrillation success. Heart rate (HR) and BP were recorded. Energy sequences were repeated after 45 mins of no intervention (Control (C), n=5), or 45 mins infusion of Diltiazem (D) (.01 mg/kg/min, n=10), or Verapamil (V) (0.1 mg/kg bolus + .01 mg/kg/min, n=10). Results (mean±SE, *=p<.01, post drug vs. pre drug):

% Defib Success:	C		D		V	
	Pre	Post	Pre	Post	Pre	Post
25J	31±19	40±17	28±7	17±6	50±14	15±2*
50J	70±20	70±18	71±9	52±14*	64±11	44±14
100J	84±12	87±13	87±9	82±11	82±9	72±13

Mean BP responses to 100J shocks were as follows (mmHg):

Time	0 Secs	15 Secs	30 Secs	60 Secs	3 Mins
C Pre	120±14	103±13	115±9	114±10	117±9
Post	119±6	106±14	119±11	115±14	113±8
D Pre	103±8	102±9	111±9	113±10	105±5
Post	92±6	64±9	84±9*	87±6*	93±6*
V Pre	106±7	108±9	118±9	113±7	104±6
Post	96±8	78±12*	84±10*	90±10*	92±8*

HR responses were not altered by D or V. Conclusions: D and V modestly reduced % success of shocks, especially at lower energy levels. BP after defibrillation was lower with D and V, indicating a blunting of the adrenergic response to defibrillation by calcium channel blockers.

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #366/367
Evaluation of Antiarrhythmic Drug Effects and Toxicity

DRUG ASSOCIATED VENTRICULAR FIBRILLATION: ANALYSIS OF CLINICAL FEATURES AND QTc PROLONGATION.
Joseph D. Minardo, M.D., James J. Heger, M.D., F.A.C.C., Douglas P. Zipes, M.D., F.A.C.C., William M. Miles, M.D., F.A.C.C., and Eric N. Prystowsky, M.D., F.A.C.C. Krannert Inst. of Cardiology, Indiana Univ. Sch. of Medicine, Indianapolis, IN.

Reports of clinical features and role of QTc prolongation in drug associated ventricular fibrillation (DAVF) have been variable. We analyzed 40 episodes of DAVF in 30 patients (pts), 17 men, 13 women, mean age 59 yr, initially treated for sustained ventricular tachycardia (VT) (3 pts), nonsustained VT (18 pts), PVCs (4 pts), atrial fibrillation (4 pts) and no arrhythmia (1 pt). DAVF occurred during quinidine treatment (Q) in 15, procainamide (PA) in 11, disopyramide (DP) in 6 and other drugs in 8 episodes. For Q, PA and DP, median duration of therapy before DAVF was 3 days. Drug serum concentrations in 15 pts were in acceptable ranges and QRS duration was .11±.03 sec. Serum K was <3.5 meq/L in 12/32 and digitalis was present during 25/40 episodes of DAVF. The QTc intervals that could be measured after DAVF in 22 pts with Q, PA or DP (Grp I) were compared with another 31 pts treated for VT with Q, PA or DP who did not develop DAVF (Grp II).

	Control QTc	Drug QTc	p value
Grp I	.45±.04	.49±.06	<.001
Grp II	.43±.03	.48±.04	<.001

Drug QTc for Grp I vs Grp II were similar although the increase from control to drug was greater in Grp II (p<.05). DAVF occurred with >1 drug in 4 of 25 pts treated with Q, PA or DP after the first episode. Chronic therapy was Q or PA in 3 pts, investigational drugs in 20 pts and no drug in 9 pts. During a mean follow-up of 25 months, 1 treated pt died suddenly. We conclude that DAVF is an early event; there is a crossover risk of DAVF with Q, PA or DP, and QTc prolongation is not predictive of DAVF.

DIFFERENT EFFECTS OF ANTIARRHYTHMIC MEDICATION ON REFRACTORINESS OF ACCESSORY AV PATHWAY AND MYOCARDIAL TISSUE

Karl-Heinz Kuck, M.D., Klaus-Peter Kunze, M.D., Angelika Costard, M.D. Michael Schlüter, Ph.D., Dept. of Cardiology, University Hospital Eppendorf, Hamburg, West Germany

To determine the effect of antiarrhythmic drugs (D) on the refractoriness of accessory AV pathways (AP) and myocardial tissue (MY), we measured the effective refractory periods (ERPs) of the AP in anterograde (ant) and retrograde (ret) direction, and of RA, LA (via coronary sinus) and RV before and after intravenous D administration. Our study population consisted of 42 consecutive patients (13 women, 29 men; mean age 38 years) with an AP, who underwent standard electrophysiologic investigation. The ERPs of MY were determined with the extrastimulus method at a paced basic cycle length of 440 ms, the ant ERP of AP during incremental atrial pacing at the site of atrial AP insertion, and the ret ERP of AP during incremental RV pacing. 14 pts received encainide (1.5 mg/kg), 15 pts propafenone (2 mg/kg), and 15 pts sotalol (1.5 mg/kg). D caused significant increases in ant ERP of AP (250 ± 46 to 315 ± 105 ms; ($p < .001$), ret ERP of AP (255 ± 48 to 316 ± 87; $p < .001$), RA (215 ± 20 to 231 ± 25; $p < .01$), and RV (218 ± 28 to 237 ± 26 ms; $p < .001$), but not in LA (245 ± 29 to 254 ± 32). Changes of ant ERP of AP were found to correlate with changes of ret ERP of AP ($r = .61$), but neither correlated with changes of ERPs of RA, LA, and RV. The increase in ERP was significantly more pronouced in ant and ret AP direction than in any site of MY ($p < .05$; Friedman test). This effect did not differ between encainide, propafenone and sotalol. ERP increase (defined as > 20 ms) in ant and ret ERP of AP was independent of D effect on MY.

Conclusions: The effect of D on ant and ret ERP of AP is significantly more pronounced as, and independent from the effect on ERP of MY.

ARE THERE CLINICAL PREDICTORS FOR ARRHYTHMIA AGGRAVATION?
William Slater, MD, Philip Podrid, MD, FACC, Steven Lampert, MD, Bernard Lown, MD, FACC, Cardiovascular Laboratories, Harvard School of Public Health & Dept. of Med., Brigham & Women's Hospital, Boston, MA

To determine if there are predictors of aggravation of arrhythmia (AgA) by an antiarrhythmic drug (AAD), we studied 51 patients (PTs) with AgA during therapy with either Quinidine, type 1A drug (N=16); Mexiletine, type 1B drug (N=13); or Encainide, type 1C drug (N=22). For each PT with AgA, two controls (N=102) who did not experience AgA with any AAD were randomly selected. Baseline evaluation of all PTs included 48 hour ambulatory monitoring, treadmill exercise test, and radionuclide ventriculogram. AgA was defined as: 1) a four-fold increase in VPB frequency 2) a ten-fold increase in repetitive forms (couplets or ventricular tachycardia (VT)) 3) the occurrence of a sustained tachyarrhythmia not present in control. The clinical variables examined included age, sex, type of heart disease, presenting arrhythmia, left ventricular ejection fraction, severity of ischemia, exercise duration, conduction abnormalities prior to drug, ECG changes during drug therapy, drug dose and blood level. The only clinical parameter associated with AgA was the type of presenting arrhythmia, i.e. ventricular fibrillation or sustained VT vs nonsustained VT or VPBs ($p<.02$).

PTs susceptible to drug-induced AgA cannot be identified by clinical criteria, electrocardiographic changes or pharmacokinetics of the AAD. This complication is however more frequent in those with a history of malignant arrhythmia and AAD must be used cautiously in such PTs.

DOES SUPPRESSION OF VENTRICULAR ECTOPIC ACTIVITY CORRELATE WITH PREVENTION OF INDUCIBLE VENTRICULAR TACHYCARDIA.
John C. Somberg, M.D., Joseph Schwartz, M.D., Vilma Torres, M.D., Jonathan Wynn, M.D., Deborah Keefe, M.D., Dennis Miura, M.D. Albert Einstein College of Medicine, Bronx, New York.

We evaluated the efficacy of antiarrhythmic agents at programmed electrical stimulation (PES) in 120 drug trials in 43 patients undergoing PES studies with cardiac arrest or sustained ventricular tachycardia (VT). Frequency of ventricular premature depolarization (VPD) was assessed by trending for 15 minutes before and after drug administration. Initial trending evaluation in 10 patients showed a significant concordance (r=0.98) between ectopy frequency and grade in 2 consecutive trending drug free periods. An increase in VPD frequency was defined as a 10 time or greater increase from baseline if mean baseline VPD frequency was 1-50 VPDs/hour and a 5 time increase if baseline VPDs are 51-100 VPDs/hour. A decrease in VPDs was defined as a 10 time or greater decrease from baseline if mean VPD frequency were 51-100/hour. The comparative results of PES testing and VPD trending showed the following:

	VPD frequency		
PES results	increased	decreased	no change
protected	14	29	11
not protected	10	27	29

There is no correlation between the effects of antiarrhythmic drug action on VPD frequency and protection against VT induction at PES (chi-square 0.37; $p<0.5$, ns). Patients could be protected (no VT provoked) at PES while having no significant reduction in VPD frequency. Reduction in VPDs can occur without protection at PES. These findings suggest that PES testing and VPD frequency measure different aspects of electrical instability.

THE EFFICACY OF DIGOXIN IN THE CONVERSION OF ATRIAL FIBRILLATION TO NORMAL SINUS RHYTHM.
Anne A. Knowlton, MD, Rodney H. Falk, MB, Ch.B, FACC, Sheilah Bernard, MD, Jean L. O'Brien, RN, Norman E. Gotlieb, MD, Nancy J. Battinelli, RN, Carl S. Apstein, MD, FACC. Boston City Hospital, Boston, MA.

Although digitalis is the standard therapy for atrial fibrillation (AF), no randomized study of its efficacy for conversion to normal sinus rhythm (NSR) has been done. Therefore, over a 20 month period, we carried out a double blind, 16 hr protocol comparing a rapidly absorbed oral digoxin with placebo in new onset AF (≤7 days) of various etiologies (valve disease, n=14, chest disease, n=11, "holiday heart", n=10, other, n=17, idiopathic, n=2 with some multiple etiologies). Patients (pts) with moderate or severe CHF, angina, hemodynamic compromise, thyrotoxicosis, or pretreated with antiarrhythmic therapy were not entered into the study. Drug was administered in a dosage schedule titrated to heart rate, starting with a loading dose of 0.6mg, with a maximal total dose of 1.2mg. All pts on digoxin achieved a therapeutic blood level (mean 1.1±0.1 SEM at 4 hrs). Pts wore Holter monitors during the 16 hr study. The results of 40 pts, 21 randomized to digoxin (mean age 59.5, 13 male) and 19 randomized to placebo (mean age 62.5, 10 male) were analyzed. Conversion to NSR occurred in 11/21 (52%) of pts on digoxin versus 8/19 (42%) of pts on placebo (NS). Mean time to conversion was 5.7 hrs in the digoxin group versus 4.0 hrs in the placebo group (p=NS). Thirty pts had adequate echoes to assess left atrial size (LA). There was no significant difference in mean LA size between digoxin (4.2) versus placebo (4.2) nor between all convertors (4.3) versus nonconvertors (4.2). We conclude that in our pts digoxin had no significant effect on conversion of atrial fibrillation to normal sinus rhythm in the first 16 hrs after presentation.

TREATMENT OF FLECAINIDE INDUCED VENTRICULAR TACHYCARDIA WITH LIDOCAINE.
Sharon R. Maza, M.D., Jonathan Wynn, M.D., Joseph Schwartz, M.D., Daniel Zanger, B.A., Deborah Keefe, M.D., Dennis Miura, M.D., John C. Somberg, M.D., Department of Medicine, Cardiology Division, Albert Einstein College of Medicine, Bronx, New York.

Flecainide acetate (F) is a new class Ic antiarrythmic agent which prolongs refractoriness and causes significant depression of the maximal rate of depolarization. When intravenous F has been used for acute drug testing during programmed electrical stimulation (PES) it has demonstrated both efficacy as an antiarrhythmic agent and potential for arrythmogenicity. We report three cases of a proarrythmic response to F which were successfully treated with lidocaine (L). All 3 cases received a 2mg/min infusion of F over 20 minutes in 4 divided doses with onset of ventricular tachycardia (VT) prior to any PES on F. In Case 1 VT was sustained and associated with hypotension and apnea which necessitated cardiopulmonary resuscitation. The patient was unresponsive to pacing techniques and multiple attempts at defibrillation. Case 2 had sustained VT. Case 3 had incessant nonsustained VT. All 3 cases responded immediately to a bolus of 100 mg of L followed by a 2 mg/min drip. In Case 1, although resumption of normal sinus rhythm occurred immediately, nonsustained VT occurred after 10 minutes which was responsive to an additional 50 mg bolus of L and the institution of the 2 mg/min drip. Lidocaine, because of its rapid onset and offset kinetics and its tendency towards decreasing the heterogenicity of refractoriness, may counteract the effects of F and may thus prove useful in the treatment of F induced VT.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #157
Valvular Heart Surgery I

COMPARISON OF OUTCOME FIVE YEARS AFTER VALVE REPLACEMENT WITH A BIOPROSTHESIS VERSUS A MECHANICAL PROSTHESIS. RESULTS OF A RANDOMIZED TRIAL. Participants in the VA Cooperative Study on Valvular Heart Disease (Report prepared by K.E. Hammermeister, M.D., FACC, Gulshan Sethi, M.D., Cecil Burchfiel, Ph.D., Julianne Souchek, Ph.D., Charles Oprian, Ph.D., Edward Folland, M.D.,FACC, Shukri Khuri, M.D., Shahbudin Rahimtoola, M.D., FACC, Thomas Tosch, Ph.D., and William Henderson, Ph.D.)

One of the major goals of the VA Cooperative Study on Valvular Heart Disease is to compare survival and incidence of valve related complications (systemic embolism, endocarditis, valve thrombosis or regurgitation, clinically significant bleeding, and reoperation for any other reason) in patients undergoing single valve replacement randomized between a bioprosthesis, the Hancock porcine valve (H, n=288), and a mechanical prosthesis, the Bjork-Shiley spherical disc valve (BS, n=287). At an average followup of 53 months there are no statistically significant differences in survival for either aortic valve replacement (AVR) or mitral valve replacement (MVR), although there is a trend toward improved survival with the mitral H versus the mitral BS (five year survival probability = 0.72 versus 0.62). Valve related complications occurred significantly less frequently in MVR with H versus MVR with BS (five year complication-free probabilities of 0.60 and 0.47, respectively; $p<.05$); similar trends were observed following AVR favoring H, but were not statistically significant. The differences in complication rates are due to increased frequency of significant bleeding with BS; however, the numbers of deaths due to bleeding were similar between the two valve types. We conclude that at intermediate duration of followup, patients receiving a bioprosthesis and a mechanical prosthesis have similar outcome, except for increased frequency of non-fatal bleeding in patients receiving BS.

FIVE-YEAR COMPARISON OF ST. JUDE AND PORCINE MITRAL VALVES
Pamela S. Douglas, M.D., F.A.C.C., John W. Hirshfeld, Jr., M.D., F.A.C.C., Richard Edie, M.D., Alden Harken, M.D., F.A.C.C., Larry Stephenson, M.D., F.A.C.C., Kathleen Gleason, L. Henry Edmunds, M.D., F.A.C.C., University of Pennsylvania, Philadelphia, PA.

To characterize performance and better guide selection of mitral valve prostheses, we prospectively examined 106 consecutive patients (pts) undergoing mitral valve replacement. Pts received either a St. Jude valve (SJV; n=68) or a porcine valve (PV; n=38) and were similar with respect to 67 clinical and operative factors, allowing comparison of valve performance as an independent variable.

Total follow-up was 3312 pt-months (mean 38 months, range 2-57 months, 93% complete). All SJV and half of PV were fully anticoagulated; an additional 29% of PV received antiplatelet agents alone. There were no statistical differences in symptomatic improvement or mortality by life table analysis. Linearized rates (per pt-year) of complications and relative risks (RR) for SJV to PV were: (all NS)

	Re-Op	Infection	Emboli	Bleeding	Late Death	Valve Failure
SJV	1.8	1.2	1.8	2.9	4.1	0.6 (thrombosis
PV	3.8	1.9	1.0	2.9	3.8	1.0 (degeneration)
RR	0.5	0.6	1.8	1.0	1.1	0.6

Anticoagulation use did not appear to affect rates of embolization in patients with porcine valves.

Despite differing anticoagulation use, rates of embolic and bleeding events in PV and SJV were similar. Given this comparable, low morbidity and mortality, the superior hemodynamics and durability of the SJV may favor its use in the mitral position.

UTILITY OF INTRAOPERATIVE COLOR DOPPLER FLOW IMAGING AFTER SURGICAL CORRECTION OF VALVULAR REGURGITATION.
Lawrence Czer, MD, FACC; Gerald Maurer, MD, FACC; Michele DeRobertis, RN; Robert Kass, MD, FACC; Myles Lee, MD, FACC; Aurelio Chaux, MD, FACC; Jack Matloff, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA.

We evaluated 2-dimensional color Doppler blood flow mapping (CFM) for detection and quantitation of valvular regurgitation before and after surgical correction in 22 pts who underwent valve repair or replacement, and in 12 control pts who had cardiac surgery without valve operation. CFM was performed intraoperatively (op) before and after cardiopulmonary bypass by placement of a 3.5 MHz transducer (Irex 880) directly on the heart; preop and 1-6 wk postop closed-chest CFM were also done. In 5 aortic, 7 mitral, 3 double St. Jude valve replacements, CFM demonstrated 3 antegrade flow jets, mild (size dependent) prosthetic regurgitation, normal bileaflet motion, and absence of paravalvular leak. Following repair of MR (2 suture annuloplasty, 2 cleft repair) and TR (2 Carpentier rings, 1 cleft repair), regurgitation decreased from 4+ or 3+ to trace or none in 6/7 by op CFM, confirmed by late postop CFM. In ischemic MR, adequacy of repair was assessed before and after vasopressor challenge, without increase in regurgitation. In 2 additional pts, LV angio was contraindicated due to LV clot or V Tach; decision was based on op CFM. Severity of valvular regurgitation (0-4+) by op CFM correlated well (R=.90) with preop cath and CFM, differing by no more than 1 grade in any pt. No complications were encountered.
Conclusion: Intraoperative CFM provides safe, accurate, and rapid assessment of valvular regurgitation and efficacy of valvular surgery, especially valve repair, prior to closure of the sternum, without use of contrast material or radiation. In selected pts valve surgery may be undertaken without preop angio.

THE REPAIR OF MITRAL INCOMPETENCE: A 16-YEAR EXPERIENCE
Mark Sand, M.D., Robert B. Karp, M.D., David Naftel, Ph.D., Eugene H. Blackstone, M.D., and John W. Kirklin, M.D., F.A.C.C., Univ of Alabama at Birmingham, Birmingham.

Between 1967 and 1985 210 patients underwent repair of mitral incompetence, either isolated or combined with other cardiac surgical procedures. Those with AV canal defects were excluded. All patients have been followed. Mean age was 49 years and the range 2.6 months to 83 years. 180 patients had annular repair, 99 had leaflet repair, 7 had tensor apparatus repair, with 74 patients having more than one of these. Actuarial survival at 2 weeks, 5 years, 10 years, and 15 years was 95% (70% CL 93%-96%), 75% (CL 71%-78%), 59% (CL 55%-64%), and 36% (CL 28%-45%). Among the subset undergoing isolated mitral valve repair between 1975 and July 1983, 5-year survival was 84% (CL 78%-88%), compared with 64% (CL 58%-69%) for patients undergoing mitral valve replacement for mitral incompetence in the same time period (P = 0.05). 38 of the 210 patients subsequently underwent mitral valve replacement, with the actuarial freedom from replacement at 2 weeks, and one, 5 and 10 years being 89% (CL 87%-91%), 88% (CL 86%-90%), 82% (CL 79%-85%), and 74% (CL 69%-78%). At the time of last followup, among the 118 patients surviving without valve replacement, 63% were in NYHA Class I, 25% in II, 6% in III, 1% in IV and 6% were undetermined; 83% were free of thromboembolism within 10 years of repair. These results indicate the wisdom of repairing mitral incompetence whenever possible.

IS MITRAL VALVULOPLASTY SUPERIOR TO MITRAL VALVE REPLACEMENT FOR PRESERVATION OF LEFT VENTRICULAR FUNCTION? AN INTRAOPERATIVE TWO-DIMENSIONAL ECHOCARDIOGRAPHIC STUDY.
Martin E. Goldman, MD, FACC, Francisco Mora, MD, Valentin Fuster, MD, FACC, Theresa Guarino, RN, Bruce P. Mindich, M.D., FACC, Mt. Sinai & St. Luke's-Roosevelt Hospitals, NY, NY.

The time course and mechanism of LV dysfunction following mitral valve replacement (MVR) has not been previously determined. In 11 patients (pts) undergoing surgery for isolated mitral regurgitation, without coronary artery disease, we used intraoperative 2-D echocardiography to evaluate the LV in the mid-papillary short-axis plane. 6 pts underwent conventional MVR and 5 pts had mitral valvuloplasty (VP). Blinded observers, calculated LV end-diastolic and end-systolic areas, ejection fractions (EF) and quadrant regional wall motion (WM) before (pre) and following (post) the MV operation. Intraoperative hemodynamics were similar in all pts.(XCLMP=Crossclamp time in minutes, **p<0.0001, *p<0.02)

	Age	PreEF	PostEF	Δ EF**	XCLMP*
MVR(6)	63±17	.66±.08	.42±.07	-.24±.06	45±10
VP(5)	61±19	.54±.02	.57±.02	.03±.04	27±9

LV EF was maintained by VP but fell significantly post MVR (p<0.0001). Despite having similar baseline LV contractility, WM fell in only 1/20 quadrants in VP pts, but decreased in 17/24 quadrants in MVR pts, especially anteroseptally (p<0.01) and posteroseptally (p<0.03). The prolonged XCLMP of MVR may contribute to LV dysfunction but should have a diffuse effect. While valvuloplasty maintains normal LV anatomy, conventional MVR alters LV geometry and may affect regional wall stress particularly along the septum, leading to LV dysfunction. Therefore, valvuloplasty by preserving LV geometry and function is superior to MVR.

OPERATION FOR HYPERTROPHIC SUBAORTIC STENOSIS IN THE AGED.
Matthew M. Cooper, M.D., Charles L. McIntosh, M.D., F.A.C.C, John P. Kupferschmid, M.D., Richard E. Clark, M.D., F.A.C.C, Surgery Branch, NHLBI, NIH, Bethesda, MD.

To determine if surgical palliation of idiopathic hypertrophic subaortic stenosis (IHSS) is worthwhile in the elderly we examined function, hemodynamic status, and survival following left ventriculomyotomy and septal myectomy (Morrow Procedure,LVMM) in 47 patients 65 years and older ($\bar{x}$=68,65-81y,♀=35). 79% (n=31) underwent postop catheterization at an average of 6 months. The average preop N.Y.H.A. functional class of 3.3±.07* improved at latest followup to 2.0±.15 (p<.001). The peak systolic left ventricular outflow tract gradient (LVOTG) at rest decreased from 71±8 to 5±2mmHg (p<.001). Mean decreases in maximal LVOTG with Valsalva, amyl nitrate, and isoproterenol were 72% (98±8→27±5mmHg), 71% (110±12→32±7mmHg), and 61% (114±9→45±8mmHg), respectively (all p<.001). There were no statistically significant differences between pre- and postop values of CO,CI,PA,LA, pulmonary wedge pressure and vascular resistance, or pulse pressure response to premature ventricular contraction. 51% (n=24) had mitral insufficiency preop, 4 (13%) postop (p<.005,Chi-square). Followup averaged 58 months (1-120 months). 3,5,7 and 9-year actuarial survival was 82±6% (n=28), 72±8% (n=17), 41± 10% (n=8), and 28±10% (n=3), respectively. Ventricular septal rupture occurred in 4 patients (8.5%), 3 of whom required coronary bypass, 2 of whom had septal morphology that would now by revised operative criteria prompt mitral valve replacement rather than LVMM, and resulted in 3 early deaths. Acute onset of a low cardiac output state (n=3) and sepsis (n=2) contributed to the hospital mortality of 17%. Coronary artery disease, present in 36% (n=17), did not contribute to hospital mortality in the absence of septal rupture. It is concluded that surgical palliation of the elderly with IHSS can be performed with significant hemodynamic and functional improvement. Long term survival at improved functional levels is attainable.
*All values mean ± S.E.M.

LATE SURVIVAL AFTER ISOLATED AORTIC VALVE REPLACEMENT FOR 236 PATIENTS;INFLUENCE OF VENTRICULAR ARRHYTHMIAS
Bruce W. Lytle, MD, FACC, John Ellis, MD, James D. Maloney, MD, FACC, Delos M. Cosgrove, MD, FACC, Marlene Goormastic, MPH, Floyd D. Loop, MD, FACC
The Cleveland Clinic Foundation, Cleveland, Ohio

To assess the influence of perioperative rhythm and arrhythmias on late survival following aortic valve replacement (AVR), 236 hospital survivors of AVR with a porcine heterograft and without significant coronary artery disease (no obstruction ≥50%) were reviewed. Preoperative and postoperative arrhythmias were sub-grouped according to the Lown classification. Follow-up at a mean interval for survivors of 62 mos.(range 28-87 mos.) documented 29 late deaths (11 non-cardiac,6 sudden) and survival of 97%, 94% and 91% at 1, 2 and 5 postoperative yrs. For 18 patients with postoperative ventricular arrhythmias of Lown classification ≥2, 5-yr. survival was 72% (p=0.0007). Other variables with univariate influence on survival included age (p=0.02), aortic valve lesion (p=0.07), atrial fibrillation (p=0.01) and anticoagulation with Coumadin (p=0.08). Multivariate testing, however, identified only advanced age (p>0.0001) and valve lesion (survival for mixed lesions >stenotic lesion (p=0.025) >insufficient lesions (p=0.0017)) as independent predictors of decreased survival. Serious arrhythmias were covariant with valve lesion; only 1 patient with a mixed valve lesion had postoperative Lown ≥2 arrhythmias. Exclusion of patients with mixed valve lesions from the multivariate model showed Lown >2 arrhythmias adversely influenced the survival of patients with pure stenotic or pure insufficient valve lesions (p=0.013). Patients without coronary artery disease undergoing AVR with a bioprosthesis have favorable late survival and a low incidence of sudden death, although the presence of serious postoperative ventricular arrhythmias predicts an increased late risk.

Wednesday, March 12, 1986
10:30AM-12:00NOON, Room #157
Valvular Heart Surgery II

PERFORMANCE OF A FABRICATED TRILEAFLET PORCINE BIOPROSTHESIS: 9-YEAR FOLLOWUP OF THE HANCOCK MODIFIED ORIFICE VALVE
Verdi J. DiSesa, M.D., Elizabeth N. Allred, M.S., Richard J. Shemin, M.D., F.A.C.C., John J. Collins, Jr., M.D., F.A.C.C., Lawrence H. Cohn, M.D., F.A.C.C.
Brigham and Women's Hospital and Harvard Medical School, Boston, MA

The fabrication of the Hancock MO valve raised questions about its long-term durability. Since 1976, 262 pts (167M/95F, 16-85, 62 yrs) underwent aortic valve replacement (AVR) using 103 21 mm, 143 23 mm and 16 25 mm modified orifice (MO) valves. There were 6 operative deaths (2.3%). 234 pts were alive 3-87 (42) mos postoperatively. Actuarial probability of survival at 60 mos was 88±3%. 221 survivors are in functional classes I or II. 29 pts have suffered valve related complications: thromboembolism in 17 (1.9%/pt yr); primary valve dysfunction (PVD) in 5 (0.6%/pt yr); and endocarditis (SBE) in 7 (0.8%/pt yr). 12 pts have required reoperation (1.3%/pt yr) for PVD (5 pts), SBE (4 pts), and perivalvar leak (3 pts). At 60 mos actuarial probability of freedom from TE was 91±3%, from PVD 95±2%, and from SBE 98±1%. Probability of freedom from all valve-related complications was 84±3% and from reoperation 93±2% at 60 mos.

Long-term performance of the Hancock MO valve justifies its continued use for AVR.

IMPACT OF CORONARY ARTERY DISEASE AND MYOCARDIAL REVASCULARIZATION ON RESULTS OF AORTIC VALVE REPLACMENT.
Lawrence Czer, MD, FACC; Timothy Bateman, MD, FACC; Richard Gray, MD, FACC; Michele De Robertis, RN; Robert Kass, MD, FACC; Aurelio Chaux, MD, FACC; Jack Matloff, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA.

In order to determine whether coronary artery disease (CAD) and myocardial revascularization (CABG) influenced survival following single aortic valve replacement (AVR) we reviewed our entire experience with AVR between 1969 and 1984. All pts over age 40 had preop coronary angiography. Of 449 total pts, 40% (180) had no associated CAD; 49% (220) had CAD and CABG; and an additional 11% (49) had unbypassed CAD. Early (30-day) mortalities were 2.3% (no CAD), 8.1% (CAD + CABG; p<.05), and 4.4% (CAD, no CABG; p=NS). Use of hypothermic cardioplegia (after 1978; N=220) reduced early mortality in pts requiring CABG (from 14.3% to 6.0%; p<.05), but had no effect in pts who had AVR alone (2.3% vs 2.9%). Pts were followed for up to 15 yrs (mean, 4.1) for a total of 1840 pt-yrs (2% lost; 98% complete). Actuarial survivals at 7 years were 80±4% (no CAD), 61±5% (CAD + CABG; p<.05), and 49±11% (CAD, no CABG). Rapid attrition was observed in the unbypassed CAD group, beginning at 4 years. The major cause of death (51%) in all groups was cardiac non-valvular (heart failure, infarction, arrhythmia, or sudden death).

Conclusions: After AVR, associated CAD has a significant detrimental affect on late (>4 yrs) survival, especially if left unbypassed; revascularization improves late survival. Early mortality has been reduced by the use of cardioplegia in pts requiring concomitant AVR and CABG.

EFFECTS OF LEFT VENTRICULAR VENTING AND DISTENTION DURING HETEROGENOUS CARDIOPLEGIC ARREST

Harold Lazar MD, Kenneth Wilcox MD, Thomas Hankins CCP, Jonathan Plehn MD, and Arthur Roberts MD, FACC, Boston University Medical Center, Boston, MA

The effects of LV venting and distention on myocardial protection during heterogenous cardioplegic arrest remain undefined. This study was undertaken to determine whether LV venting and distention during arrest alter LV cooling and the recovery of postischemic global and regional LV function. Twenty-one pigs were placed on bypass and subjected to 80 minutes of ischemic arrest with the mid LAD occluded. Hearts were protected with multidose potassium, crystalloid cardioplegia supplemented with topical and systemic (28°C) hypothermia. During arrest, the LV was vented in 7 pigs; 7 pigs were unvented, and in 7 others, the EDP(end-diastolic pressure) was maintained at 15mmHg. We measured stroke work index (SWI), compliance (EDV-EDP curves), wall motion (2-D echo), LV temperature in the LAD region, and LV EDP(Millar catheter). Results are: Mean ± SE, *EDP = 10mmHg, +$p < .05$ vs vented and nonvented.

	Vented	Non-Vented	Distended
EDP during arrest (mmHg)	0.8±0.1	3.7±1.7	15.0±0.5*
LV temperature(°C)	14.2±0.7	15.5±1.2	10.1±1.8*
Postischemic SWI(g-m/kg)*	.62±.07	.66±.07	.78±.09
EDV(ml)Preischemia*vs	61±10	55±5	42±4
Postischemia*	59±9	60±7	45±5
Wall Motion Score (0=Normal to 36)	5.5±1.8	4.8±.12	.07±.04+

LV venting failed to lower LV temperature or improve regional (wall motion) and global (SWI) function. Distended hearts had the lowest LV temperature, highest SWI and best wall motion scores. We conclude that LV venting during heterogenous cardioplegic arrest does not enhance myocardial protection and may negate the beneficial effects of moderate (EDP=15mmHg) LV distention.

CAN DIMETHYL SULFOXIDE (DMSO) PROLONG THE ISCHEMIC TOLERANCE OF THE SPINAL CORD?

Kok H. Lim, M.D., Maurice Weiss, B.S, Mark Connolly, M.D., Daniel Rose, M.D., Israel Jacobowitz, M.D., Joseph Cunningham Jr., M.D., Maimonides Medical Center, Brooklyn, NY 11219

We investigated the use of dimethyl sulfoxide (DMSO) as a pharmacological means to prolong the ischemic tolerance of the spinal cord. Somatosensory evoked potential (SEP) were obtained in 14 dogs. Spinal cord ischemia was produced by placing an aortic crossclamp (AXC) just distal to the origin of the left subclavian artery. Serial SEPs were determined at 1 minute intervals until the SEP became flat line, and the AXC was continued for an additional 10 min.. In Group I (control, n=8), no medication was given following the release of the AXC. In Group II (DMSO n=6), dimethyl sulfoxide, 1 gm/kg, was administered intravenously before the removal of the AXC. The neurological status was assessed postoperatively by using the Tarlov's criteria.

Results are summarized:

	Group I (n=8)	Group II (n=6)
Aortic crossclamp (min.)	23.7 + 2.1	24.1 + 2.9
Neurological status (no. of dogs)		
paraplegia/paraperesis	8	0
complete recovery	0	6
Return of postop. SEP	No	Yes

Group I (control) animals had a significantly higher incidence of paraplegia than Group II (DMSO) animals ($p<0.001$, Fisher Exact test). In the DMSO treated group the SEPs returned in the early postoperative period within 60 minutes.

We conclude 1) DMSO can prolong the ischemic tolerance of the spinal cord, and 2) this agent may be useful as a pharmacological adjunct to decrease the incidence of paraplegia in surgery on aneurysms of the thoracic aorta.

PARAPLEGIA ASSOCIATED WITH AORTIC RESECTION AND THE LAW.

Safuh Attar, M.D., F.A.C.C. and Javaid Hosnain, M.D., University of Maryland School of Medicine, Baltimore, MD

Surgeons undertaking resection of thoracic aortic aneurysms have become a target for malpractice because of the associated paraplegia (3-16%). Patients who underwent resection of thoracic and thoraco-abdominal aortic aneurysms over the last 28 years were reviewed. There were 16 patients with associated neurological changes and paraplegia. The patients ranged in age from 17-75 years. The diagnoses were: traumatic aortic aneurysm 2, thoracic arteriosclerotic aortic aneurysm 6, thoraco-abdominal aortic aneurysm 2, coarctation of aorta 2, and aortic rupture 4. Discriminate analysis of the factors contributing to paraplegia were analyzed. They were sex, age, extent of disease, number of intercostal arteries sacrificed, use of shunt, use of cardiopulmonary bypass, and hypotension. The factors that were most significant were hypotension and extent of disease. In comparison, in 35 cases of traumatic aortic ruptures, resection with shunts or partial cardiopulmonary bypass was performed on 25 patients. Ten patients underwent resection without adjunctive support. The incidence of paraplegia was similar for both groups. Also, fifty aneurysms of various etiologies were reviewed. Thirteen patients underwent surgery without adjunctive support. Thirty-seven patients utilized cardiopulmonary bypass and shunts. Again the incidence of paraplegia was similar in both groups. Currently there is no monitoring system that would predict the unequivocal occurrence of paraplegia or other neurological deficit. Paraplegia and neurological deficits following thoracic and thoraco-abdominal aortic aneurysm surgery are an inherent event of the surgical procedure that should be accepted as a potential risk and not a cause for litigation and malpractice.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #267
The Exercise Electrocardiogram

INCREASE IN S WAVE AMPLITUDE - A SENSITIVE MARKER OF ACUTE MYOCARDIAL ISCHEMIA?

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The role of changes in QRS amplitude in detecting acute myocardial ischemia is controversial.The anecdotal observation of an increase in S wave amplitude associated with ST segment depression (ST↓) during episodes of both spontaneous and exercise induced myocardial ischemia led us to investigate this phenomenon more comprehensively. In 50 patients (pts) with effort angina,severe coronary artery disease and a positive exercise test (ET),we assessed the relation between changes in S and R wave amplitude and ST↓ during exercise induced myocardial ischemia.ET was performed using a commercially available computerized system and the modified Bruce protocol.The lead group with maximum S wave amplitude in the basal state and diagnostic ischemic ST↓ during ET was selected.Measurements of S and R wave amplitude,heart rate and ST↓ were made at 1 min intervals during control,exercise and recovery.With ET all pts developed ST↓ (0.19±0.062 mV,mean ± S.D.,range 0.11 to 0.32 mV).In 49 out of the 50 pts an increase in S wave amplitude was observed,whilst R wave amplitude increased in 25,decreased in 20 and was unchanged in 5.Mean S wave amplitude increase was 0.26±0.14 mV (range 0.05 to 0.5 mV). Within individual pts,the magnitude of the increase in S wave amplitude was proportional to the severity of ST↓ (analysis of covariance: $p < 0.001$) but there was no relation to change in heart rate.

We conclude that an increase in S wave amplitude is almost invariably observed during diagnostic ST↓ in the absence of consistent R wave changes.Our findings suggest that an increase in S wave amplitude may be an additional marker of acute myocardial ischemia and its usefulness in this regard warrants further investigation.

PROLONGED POSTEXERCISE ST SEGMENT DEPRESSION IS AN INDICATOR OF HEMODYNAMICALLY SEVERE AND EXTENSIVE CORONARY ARTERY DISEASE (CAD). Steven Reisman, MD; Alan Rozanski, MD; Jamshid Maddahi, MD, FACC; Daniel Berman, MD, FACC. VA Med Ctr, Long Beach, & Cedars-Sinai Med Ctr, Los Angeles, CA

To determine the significance of prolonged post (p) exercise (Ex) ST depression (ST↓), we studied 81 patients with ≥1 mm ST during Bruce protocol treadmill Ex who underwent Ex Tl-201 scintigraphy and coronary angiography. Three-view Tl scintigrams were divided into 15 segments (segs). The extent of myocardium with Tl ischemia was determined by the number (#) of reversible segs. Forty-six patients had "normalization" of ST↓ to <1mm within the first 5 min pEx (GpI) and 35 patients had prolonged ≥1mm ST for ≥5 min pEx (GpII). Results:

	Ex Dur	# Rev Segs	Sig V	Cr V	Max Ex ST↓
GpI	9.0±3.4	2.1±2.1	2.0±1.1	1.2±1.1	2.0±0.9
GpII	6.9±2.5*	3.5±3.1*	2.5±0.9*	1.7±1.1*	2.7±1.3*

*p<0.05 vs GpI, Dur=duration (min), Rev=reversible, Sig V=# vessels with ≥50% stenosis, Cr V=# with ≥90% stenosis. Max=maximum. Triple-vessel stenosis (≥50%) was more common in GpII vs GpI (69% vs 41%, p<.05). Severe exertional hypotension (drop below resting BP) was also more common in GpII vs GpI (29% vs 9%, p<.05). Onset of 1mm ST↓ was earlier in GpII vs GpI (3.3± 1.9 min vs 6.2±3.3, p=.0001). Thus, compared to patients with early pEx ST normalization, those with prolonged pEx ST↓ manifest more extensive and severe: 1) anatomic CAD, 2) Tl and Ex ECG ischemia, and 3) physiologic and hemodynamic abnormalities. These data suggest that assessment of the duration of postexercise ST depression aids in identifying the extent and severity of CAD and of exercise-induced ischemia.

IMPROVED DETECTION OF TRIPLE VESSEL DISEASE USING ISCHEMIC AND HEMODYNAMIC VARIABLES DERIVED FROM EXERCISE TESTING

David Mannering BSc, David Bennett FRCP, David E. Ward FACC, Keith Dawkins MD, Hannah Valantine MRCP and Mark Dancy MRCP. St George's Hospital and Medical School, London, ENGLAND.

There is increasing evidence that patients at high risk after acute infarction can be identified by their response to exercise. We have undertaken ECG exercise stress testing in 213 patients 18-21 days post infarction using the Bruce protocol with BP measured at rest and peak exercise. 40% (86) had ≥1mm ST depression 80mS after the J point in 1 or more leads which was categorized into upsloping, horizontal or downsloping complexes Of this group, 76 underwent coronary angiography

The rise in systolic BP was 23 ±2.6% for single vessel disease (SVD)[n-29], 17 ±4.5% for double vessel disease (DVD) [n-15] and 7 ±3.0% for triple vessel disease (TVD) [32] (p<0.001). Onset time to 1mm ST segment depression was 5.5 ±0.4 min for SVD, 3.2 ±0.4 for DVD and 2.1 ±0.3min for TVD (p<0.001). ST segment depression recovery time after exercise was 4.2 ±0.8min for SVD, 5.2 ±0.8min for DVD and 7.9 ±0 5 min for TVD (p<0.01). Downsloping ST depresssion was associated with TVD whereas upsloping ST depression was associated with SVD (p<0.001) The sensitivity and specificity of these variables for detection of TVD is thus:

	Onset Time (<3min)	Recovery Time (>6min)	% increase in SBP (<10%)	Downsloping ST depression
Sensitivity	85%	75%	69%	56%
Specificity	90%	84%	79%	94%

Conclusions. Although the presence or absence of ST segment depression is a poor predictor of the severity of coronary artery disease, the association of ST morphology, onset time and recovery time together with the exercise BP response can identify severe coronary vessel disease.

EXERCISE ST ELEVATION: A RELIABLE GUIDE TO CORONARY ANATOMY Daniel B. Mark, M.D., David B. Pryor, M.D., Mark A. Hlatky, M.D., F.A.C.C., Kerry L. Lee, Ph.D., Frank E. Harrell, Jr., Ph.D., Robert M. Califf, M.D. Duke University Medical Center, Durham, N.C.

To determine the coronary anatomy associated with different patterns of exercise ST changes, we studied 432 consecutive patients (pts) with a Bruce treadmill and 1 vessel coronary disease (≥ 75%) stenosis). Peak exercise-induced ST deviation ≥ .10 mV was measured with a calibrated grid in each of the 12 standard ECG leads. Pts with ST elevation in leads showing an old Q wave myocardial infarction as the only exercise change were excluded. ST changes were classified as elevation or depression and by lead group involved: anterior (ANT), V1-V6, I, AVL; inferior (INF), 2, 3, AVF.

		LAD (n = 229)	RCA (n = 137)	LCX (n = 66)
ANT	ST ↓(n=104)	47 (45%)	36 (35%)	21 (20%)
INF	ST ↓(n=72)	40 (56%)	22 (30%)	10 (14%)
ANT	ST ↑(n=25)	22 (88%)	3 (12%)	--
INF	ST ↑(n= 5)	--	4 (80%)	1 (20%)*

*Left dominant circulation ↓= depression ↑= elevation LAD = left anterior descending RCA = right coronary artery LCX = left circumflex

ANT ST elevation indicated a proximal LAD lesion in 18/25 (72%), a 95% LAD stenosis in 16/25 (64%), and a proximal 95% LAD stenosis in 12/25 (48%). INF ST elevation indicated a 95% stenosis of the dominant artery in 4/5 (80%) of cases.

In summary: 1) exercise ST depression patterns do not correlate with expected coronary arterial lesions; 2) exercise ST elevation is a reliable marker of the vascular territory at risk and often indicates a proximal and/or severe stenosis.

IMPROVED ACCURACY OF TREADMILL EXERCISE TESTING IN PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY (LVH). Milton Hollenberg, MD, Julio Tubau, MD, Barry Massie, MD, FACC, Judith Wisneski, MD, FACC, and Edward Gertz, MD, FACC, VAMC and UCSF, San Francisco, CA.

Exercise testing in patients (pts) with LVH yields many false positive responses, caused largely by tall R waves that exaggerate the degree of exercise-induced ST depression. To improve test accuracy, 23 pts with LVH and chest pain were studied with a quantitative Treadmill Exercise Score (TES) that adjusts the ST depression for R wave height and for workload. Sixteen of the pts had coronary artery disease (CAD) by coronary arteriography and 7 pts had none. In 13 of the 16 LVH pts who had 3 vessel disease TES averaged 30 units while it averaged only 3 units in the 7 pts without CAD (normals without LVH and CAD fall below 4 units). All LVH pts without CAD had TES <11 whereas 15/16 pts with CAD had TES >11 (P<0.0001). Thus, TES clearly separated LVH pts with and without CAD. We studied another 19 pts with hypertension and mild LVH, but with no symptoms. All had normal nuclear wall motion and thallium stress tests (and thus had <1% probability of CAD). All had normal TES. Thus, when pts from both groups (i.e., with and without symptoms) were combined, TES was <11 in 25/26 pts with no CAD and >11 in 13/14 pts with 2 or 3 VD, P<.0001. By contrast, standard criteria classified many of the 26 LVH pts without CAD as positive: ST depression >1 mm in 14, >1.5 mm in 5, and >2 mm in 4. Thus, even in pts with LVH (many of whom had ST-T wave changes on the resting ECG), TES displays good sensitivity and specificity and allows better separation of patients with and without CAD than do standard exercise-ECG criteria.

TREADMILL ST DEVIATION PREDICTS SURVIVAL
Daniel B Mark, M.D., David B Pryor, M.D. Frank E Harrell, Ph.D., Kerry L Lee, Ph.D. Mark A Hlatky, M.D., F.A.C.C., Robert M Califf, M.D. Duke University Medical Center, Durham, N.C. 27710

To investigate whether exercise treadmill (TM) ST segment deviation adds prognostic information to clinical and cardiac catheterization (CATH) data, 2722 consecutive medically treated patients (pts) with a Bruce TM and CATH within 6 weeks were followed for up to 10 years (median follow-up 5 years). Surgically treated pts (n=627) were included only until the date of operation. All exercise-induced ST deviation ≥ .10 mV was measured with a calibrated grid. ST depression ≥ .20 mV occurred in 12% of pts. ST elevation ≥ .20 mV occurred in 2% of pts.

Survival probabilities (unadjusted Kaplan-Meier estimates) were:

	1 year	5 years	9 years
No ST deviation	.99	.95	.93
ST .10 - .15 mV	.97	.91	.85
ST ≥ .20 mV	.93	.77	.63

Using the Cox regression model, ST deviation added independent prognostic information after adjusting for clinical variables (including anginal pain course) and CATH variables (including coronary anatomy and ventricular function) (p=.004). A .20 mV or more ST deviation considered alone was associated with a ≥ 3-fold increase in the mortality rate relative to a negative test. After adjustment for clinical and CATH data, the same TM ST response predicted a ≥ 50% mortality increase. In summary: 1) marked ST deviation identifies a high risk subgroup of pts; 2) TM ST segment deviation adds prognostic information to clinical and catheterization data.

BLOOD PRESSURE VARIABILITY IN ADOLESCENTS OF HYPERTENSIVE AND NORMOTENSIVE PARENTS.
Charlotte Ferencz, M.D., F.A.C.C., Joel I.Brenner, M.D., F.A.C.C., Patricia C.Dischinger, Ph.D., and P. David Wilson, Ph.D., University of Maryland School of Medicine, Baltimore, Maryland.

A population-based epidemiological study investigated the hypothesis that 24-hour BP recordings can differentiate children of a hypertensive parents (cases) from children of normotensive parents (controls). Adolescents, 13-19 years of age were drawn from a representative sample of Maryland households in which BP was measured in the adults. Utilizing the Avionics Pressurometer III 24-hour BP recordings fulfilled rigid quality standards in 178 children. BP levels were evaluated for sleep and wake (school hours/non-school hours) periods. A diary of activities and a questionnaire provided co-variate data. For each child frequency distributions of the BP measurements were constructed for each time period and descriptors of the distributions (mean, median, spread, 90%-ile, skewness) were used in multiple linear and logistic analyses. The manual BP at onset could not discriminate between cases and controls whereas ambulatory BP clearly did, mainly during waking hours. Although all subjects were normotensive, systolic and diastolic BP descriptors showed a significant dependence on case-control status in interaction with sex and weight. Since manual BP could not discriminate between cases and controls, the 24-hour ambulatory measurements represent an as yet untapped resource for childhood studies.

Supported by NHLBI HL 25876

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #267
Coronary Heart Disease: Prevention

THE COST OF ADULT CARDIOVASCULAR DISEASE
William R. Harlan, M.D., J. William Thomas, Ph.D., and Hillary A. Murt, Ph.D., University of Michigan, Ann Arbor.

Cardiovascular disease has a profound national impact on the cost of health care and accounted for $50 billion in health charges in 1980. The distribution of health expenditures reflects the demands for health services and can help define strategies to improve accessibility and care. The National Medical Care Utilization and Expenditure Survey (NMCUES) of 1980 provides the only comprehensive assessment of service utilization and care costs for the civilian, non-institutionalized U.S. population. These data were used to determine the health care costs for hypertension and other cardiovascular disease and to compare these with health care costs for the general population. Persons reporting cardiovascular diseases accounted for over 32% of national health care charges, 25% of all ambulatory visits, 39% of all hospital days, and reported 30% of all disability days. There were important differences among categories of cardiovascular diseases. Hypertension was associated with only slightly greater costs and functional disability. Per capita costs were only $142 greater than health costs for the general population and hypertensives had disability measures that were slightly higher. However, other cardiovascular conditions had per capita medical costs and disability days that were ten times higher than for hypertension or for the general population. There were no significant differences by gender, race or family income in medical costs for cardiovascular disease suggesting no major impediments to obtaining care. The tenfold greater costs when cardiovascular disorders complicate hypertension confirm the minimal cost of treatment and document the cost effectiveness of hypertension treatment.

AN OVERVIEW OF TRIALS OF PHARMACOLOGIC THERAPY OF MILD HYPERTENSION.
Pat Hebert, Ph.D., James O. Taylor, M.D., Charles H. Hennekens, M.D., (Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Beth Israel Hospital, Harvard Medical School, Boston, MA 02115).

Despite the availability of data from 6 community-based randomized trials on over 33,000 patients with diastolic blood pressures from 90 to 119 (of which 4 were ≤ 114), the value of treatment of mild hypertension with drugs remains debated.

To obtain an overview we pooled the data and found that those receiving pharmacologic treatment experienced an overall 13% reduction (RR=0.87) in total mortality which was statistically significant (95% confidence limits from 0.79 to 0.97). Further, for total cardiovascular (CV) mortality the pooled RR was 0.8 (0.7, 0.9). As regards specific CV mortality endpoints, the largest benefit was seen in fatal stroke (RR=0.6, 0.5 to 0.8) whereas for fatal MI the reduction was not statistically significant (RR= 0.9, 0.7 to 1.1).

In further analyses restricted to entry DBP's ≤ 109 the RR for total mortality was 0.87 (0.77 to 0.98). For fatal strokes the magnitude and significance of the reduction was somewhat less (RR=0.7, 0.5 to 1.0) and the fatal MI effect remained not significant (RR=0.9, 0.7 to 1.1).

This overview (of 6 trials of patients with entry DBP levels from 90 to 119) indicates a significant benefit of pharmacologic treatment of mild hypertension on total mortality, total CV mortality as well as fatal and nonfatal stroke. These benefits were somewhat less but still present for those with entry level DBP ≤ 109. The data suggest that previously reported null results of individual trials may have been due to inadequate power to detect small to moderate but clinically worthwhile effects of pharmacologic treatment of mild hypertension.

CLINICAL AND ECHOCARDIOGRAPHIC RISK FACTORS FOR SYSTEMIC EMBOLIZATION IN PATIENTS WITH ATRIAL FIBRILLATION IN THE ABSENCE OF MITRAL STENOSIS

Nicholas A. Ruocco, Jr., M.D., Albert S. Most, M.D., FACC, Rhode Island Hospital, Brown University, Providence, Rhode Island

A significant risk of systemic embolization has been demonstrated in patients (PTS) with atrial fibrillation (AF) even in the absence of mitral stenosis (MS). Since anticoagulation to prevent embolization carries significant morbidity and mortality, we carried out a risk stratification analysis to determine which PTS should receive chronic anticoagulation therapy for AF. Clinical and echocardiographic data, with a special emphasis on left atrial size, were reviewed in 202 PTS with new onset, chronic or paroxysmal AF who did not have MS. 59 (29%) of the PTS had an embolic event within 3 months of their echocardiogram and all were in AF at the time of embolization. Of the clinical characteristics evaluated (tobacco use, diabetes mellitus, age 65 or older, hypertension, congestive heart failure, myocardial infarction and coronary artery disease) only hypertension and age were significant risk factors for embolization (P = 0.001 and 0.01 respectively). Left atrial size, mitral annular calcification, mitral valve prolapse, normal or abnormal aortic valve and normal or abnormal left ventricle were the echocardiographic findings evaluated. Only left ventricular (LV) segmental wall motion dysfunction was a significant risk factor (P = 0.04). Mean left atrial size in PTS with an embolic event was 44.5 mm compared to 43.5 mm in the control group, P=0.43. In summary, PTS with AF in the absence of MS are at greater risk to embolize if they are 65 or older, have a history of hypertension or an LV segmental wall motion abnormality on their echo. Chronic anticoagulation should be strongly considered in this group. Left atrial size, on the other hand, is not a significant variable in determining the risk of an embolic event.

SUDDEN DEATH RISK IN OVERT CORONARY HEART DISEASE: THE FRAMINGHAM STUDY.

William B. Kannel, M.D., F.A.C.C., Ralph B. D'Agostino, Ph.D., and L. Adrienne Cupples Ph.D., Boston University Medical Center, Boston, Massachusetts

Over 30 years of follow-up of persons initially free of coronary heart disease (CHD) there were 160 sudden deaths (SD) in men and 73 in women. Of these, 55% in men and 67% in women occurred without intervening overt CHD. The proportion of coronary attacks in men presenting as SD increased from 13% at age 45-54 to 20% at age 75-84. In those with interim CHD, SD incidence was 3-6 fold greater than in those without intervening CHD whether the clinical manifestation of CHD was angina or myocardial infarction. Silent or unrecognized myocardial infarctions have the same SD risk as symptomatic recognized infarctions. Curiously, the fraction of CHD deaths which were sudden was lower in those with interim CHD (37%) than in those without prior CHD (48%). The proportion of CHD deaths as SD declined with age in men with interim CHD. Although the relative risks of SD conferred by CHD were similar in the two sexes, having CHD did not eradicate the female advantage over men in absolute SD incidence.

Once CHD appeared, only systolic pressure in men and diabetes and cigarette smoking in women remained significant predictors of SD. Cardiac failure and ECG-LVH also predisposed to SD in men with intervening CHD. The proportion of CHD deaths as SD has not declined over 3 decades despite a national decline in overall CHD mortality.

MORTALITY PREDICTORS IN SURVIVORS OF MYOCARDIAL INFARCTION. THE BHAT PLACEBO GROUP.

John B. Kostis, M.D., F.A.C.C. Robert P. Byington, Ph.D., Sidney Goldstein, M.D., F.A.C.C., Robert Peters M.D., Marvin L. Murphy, M.D., F.A.C.C. for the BHAT Study Group.

During 12 to 40 (mean 25) months of follow-up of 1921 survivors of acute myocardial infarction total mortality was 9.8% (2.6% in 3 months, 4.2% in 6 months), instantaneous mortality was 3.5% and non-sudden atherosclerotic mortality was 3.9%.

Total mortality was associated at baseline (z>2.5) with factors reflecting large myocardial damage (heart failure, relative risk=rr=2.29, prior infarction rr=2.12 cardiomegaly rr=1.97, digitalis rr=2.49, diuretics rr=1.83, high LDH rr=2.48); myocardial ischemia (ST depression rr=1.93, angina rr=1.56, prior beta blocker use rr=2.29); arrhythmias ($\geq$10 VPB/hour rr=2.35 on 24 h ambulatory ECG, use of antiarrhythmics rr=1.53); age 60 rr=2.0; black race rr=1.72; and low level leisure physical activity rr=1.70.

By multivariate analysis using 20 variables the following factors appeared to be independently associated (z> 2.5) with total mortality: ST depression, cardiothoracic ratio, peak LDH, smoking, prior use of beta blockers, hematocrit, $\geq$10 VPB/h.

Traditional risk factors were associated with non-sudden atherosclerotic death (smoking, z=3.12, cholesterol z=3.09, diabetes, z=2.47) while congestive heart failure (z=4.26) systolic blood pressure (z=2.67) ST depression (z=2.64) and prior myocardial infarction (z=2.48) were associated with instantaneous death.

Wednesday, March 12, 1986
8:30AM–10:00AM, Room #268
Ischemia and Electrical Instability

Sarcoplasmic Reticulum Calcium Release and Ischemic Ventricular Arrhythmias In Rat Heart

FT Thandroyen, MD, J. McCarthy, B.Sc., LH Opie, MD. MRC Heart Research Unit, University Cape Town, South Africa, *University Texas Health Science Center and VAMC, Dallas, TX.

We investigated the possible role of release of Ca^{2+} from sarcoplasmic reticulum (SR) in genesis of ventricular arrhythmias during 30 mins left main coronary artery ligation (CAL) in isolated rat hearts. In control series all 13 hearts developed ventricular premature beats (VPB number $225^{\pm}51$), and ventricular tachycardia (VT duration $123^{\pm}21$secs); 5 hearts developed ventricular fibrillation (VF). Ryanodine 10^{-9m} to 10^{-7m} which inhibits release of Ca^{2+} from SR prevented all arrhythmias eg $R10^{-8m}$ VPB 5/13, VT 1/14, VF 0/14 (each $p<0.01$ vs control). Ryanodine decreased left ventricular dP/dt + ve (mm Hg/sec) at 15 minutes; 10^{-9m}, $1364^{\pm}40$; $10^{-8}{}_{m}$ $1111^{\pm}108$ (each $p<0.01$ vs control $1585^{\pm}52$. R 10^{-8m} but not 10^{-9m} impaired LV relaxation. R did not preserve ischemic tissue ATP, glycogen or reduce tissue lactate or cyclic AMP. Heart rate and coronary perfusion was unchanged. Caffeine 10^{-2m} which decreases Ca^{2+} release from SR (by enhancing release and decreasing reuptake) prevented VT, 3/10 vs 13/13 and VF 0/10 vs 5/13; each $p<0.01$ vs control. Caffeine decreased ischemic tissue energy stores and increased tissue cyclic AMP. We suggest that release of Ca^{2+} from sarcoplasmic reticulum may play an important role in ventricular arrhythmogenesis during acute myocardial ischemia. Ryanodine by modifying intracellular Ca^{2+} flux may be prototype for new class of antiarrhythmic agent.

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DOES INCREASED ADRENERGIC RECEPTOR DENSITY HELP MAINTAIN SYMPATHETIC ACTIVITY IN THE ISCHEMIC MYOCARDIUM?

Junichi Hayashi, M.D., Ryuichi Matsuo, M.D., Hideharu Manabe, M.D., Yoshizumi Habuchi, M.D., Akihiko Miyakawa, M.D., Yoshio Watanabe, M.D., F.A.C.C., Cardiovascular Institute, Fujita Gakuen Health University, Toyoake, Aichi, Japan.

To test the hypothesis that an enhanced adrenergic receptor function maintains sympathetic activity in acutely ischemic myocardium, we studied the relationships between the kinetics of beta and alpha-1 receptors and electrophysiologic parameters such as excitability threshold and conduction time in ischemic(IZ) and normal zones(NZ) in 12 dogs. Conduction time was prolonged by 12±20% in IZ 15 minutes after a left anterior descending coronary artery ligation. This trend was maintained up to 60 minutes (20±24%), while conduction time in NZ was not changed. Excitability threshold was elevated in IZ from 0.11±0.01mA to 0.16±0.01mA after 45-60 minutes of ischemia ($p<0.05$), but not in NZ. After 60 minutes of ischemia, left stellate stimulation(SS) normalized the elevated excitability threshold in IZ ($p<0.05$) and slightly reduced the prolonged conduction time in IZ. With phenol application after 60 minutes of ischemia, blocking the sympathetic nerves into IZ, excitability threshold and conduction time in IZ were further increased. SS and phenol did not change excitability threshold and conduction time in NZ. Receptor binding assay showed that the beta receptor number was significantly higher in IZ than in NZ (368±27 vs 251±16 $x10^{-16}$M/mg · protein, $p<0.05$), and so was the alpha-1 receptor number (667±146 vs 465±52, $p<0.05$). However, their affinity was not altered. Thus, a homeostatic mechanism at the receptor site appeared to maintain sympathetic activity under ischemia.

EFFECTS OF PRETREATMENT WITH PROPRANOLOL ON MYOCARDIAL β-ADRENOCEPTORS DURING ACUTE ISCHEMIA

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Chronic β-blockade is used to prevent acute ischemia, but few data exist on the effects of such therapy on β-receptors either in normal (N) or ischemic (I) myocardium. We infused propranolol 1.0 mg/kg for 6-8 days in 4 beagles. β-blockade was confirmed by a blunted HR response to isoproterenol. Five dogs served as controls. Myocardial blood flow was measured by microspheres before and 1 hr after left anterior descending coronary artery ligation. The central endocardium of the grossly cynotic area was selected for blood flow and receptor analysis. The opposite normal myocardial wall served as an additional control. In the β-blocked dogs, blood flow was reduced from 0.52±0.20 (SD) to .025±0.025 ml/min/gm wet weight ($p<.025$). In the opposite normal wall pre- and post-ligation values were 0.56±0.15 vs 0.64±0.23 ml/min/mg wet weight (p=NS). Values in control dogs were not different. β-receptor density (^{3}H-dihydroalprenolol) was not increased by 1 hr of I in control dogs when I and N myocardium were compared (7.22±1.4 vs 6.70±1.1 pmol/mg DNA). Chronic propranolol treatment also did not affect β-receptor density in N or I myocardium compared with control dogs. However, antagonist K_d increased in both N and I myocardium after β-blockade compared with control dogs (23.0±13.3 vs 5.49±2.55 and 17.5±8.9 vs 7.53±3.42 nM, both $p<.05$). We conclude: 1) contrary to prior reports acute I does not increase β-receptor number; 2) both in N and in severely I myocardium, chronic β-blockade produces decreased antagonist affinity without alterations in receptor density.

THE DEPENDENCE OF REENTRY ON THE SITE OF STIMULATION IN THE ISCHEMIC CANINE VENTRICLE.

William B. Gough, Ph.D., Mark Restivo, M.S., Vijayanand Kowtha, M.S., Mahshid A. Assadi, M.D., Nabil El-Sherif, M.D., F.A.C.C., SUNY Downstate and VAMC Brooklyn, N.Y.

It has previously been shown that a premature beat, S_2, from the right ventricular outflow of the canine heart, 4 days post infarction, produces an arc of functional conduction block (arc) around which activation slowly conducts in a figure of 8 pattern and reenters. The spatial gradient of effective refractoriness (ERP) that occurs around the border of the IZ comprises the functional substrate for the arc. Isochrones of ERP appear as concentric rings which increase from the border to the core of the IZ. This study determined how the arc depended on the sight of stimulation (SOS) when sites circumscribing the IZ were tested. In 9 dogs showing epicardial reentry, the ERPs (2x diastolic threshold) were determined at all 62 recording sites. There were two types of responses observed. At moderate gradients (20-50 msec/cm) the arc centered opposite the SOS and rotated as the SOS was rotated. However, at severe ERP gradients (50-110 msec/cm) the arc changed little when the SOS was rotated because the time of conduction around the IZ was still shorter than the recovery of excitability of sites forming the arc. Consequently, the reentrant pattern changed little. Therefore, 1) The morphology of the arc may vary as a function of SOS. 2) The isochrones of ERP determine the arc regardless of the fiber orientation between the SOS and the IZ (all fiber orientations between the SOS and IZ were encountered with SOS rotation). Thus, the interaction of SOS and ERP patterns determine the inducibility of reentry. These principles may apply to the choice of SOS and inducibility of ventricular reentry in man.

SUPERSELECTIVE ACTION OF BRB-I-28 ON AUTOMATICITY AND CONDUCTION IN NORMAL AND INFARCTED DOG HEARTS

Benjamin J. Scherlag, Ph.D., F.A.C.C., Eugene Patterson, Ph.D., LuZhi Guo, M.D., M. Daniel Thompson, Ph.D., and K. Darrell Berlin, Ph.D. University of Oklahoma Health Sciences Center and VAMC, Oklahoma City, OK.

Previously we found a new antiarrhythmic (AA) agent BRB-I-28 had significantly better AA effects than lidocaine (L). To study the basis of these effects, complete heart block was induced by AV nodal (AVN) damage in 9 anesthetized dogs. The idioventricular rate (IVR) averaged 42±6/min. After intravenous L, 3 and 6 mg/kg, IVR was reduced to 32±11/min, p=0.04 and 21±9/min, p=0.009, respectively. BRB-I-28, 3 and 6 mg/kg had no significant effect on IVR, 41±9/min and 41±6/min. In 10 dogs, 24 hours after left anterior descending coronary artery ligation, atrial pacing and His bundle recordings were used to determine AVN and His-Purkinje conduction times. Only L, significantly depressed AVN conduction. Wenckebach cycles (WC) occurred at 321±14/min during control pacing and were unchanged after BRB-I-28, 6 mg/kg. After L, 6 mg/kg, WC were seen at 274±21/min. Neither BRB-I-28 nor L significantly affected His-Purkinje conduction. Vagal induced slowing of the sinus rate unmasked accelerated IVR, 145±20/min which was slowed by L, 125±23/min, p=0.05 but was unaffected by BRB-I-28, 138±19/min, p=0.5. BRB-I-28 prevented inducible, reentrant ventricular tachycardia (RVT) in 3/8 dogs; L in 0/8; and BRB-I-28 slowed RVT by 66/min whereas L slowed VT by only 35/min. Unlike L which depresses automaticity and conduction in normal and infarcted hearts, BRB-I-28 inhibits the induction of reentry in infarcted hearts and has no effects on normal or abnormal automaticity. Its selective depression of slow conduction only in abnormal tissues appears to account for its AA action.

EFFECTS OF VENTRICULAR ECTOPY ON MYOCARDIAL INFARCT SIZE IN DOGS.
Stanley Nattel, M.D., F.A.C.C., Scott Beau, and Gary McCarragher, B.Sc., McGill University, Montreal, Canada.

Tachycardia is known to increase the size of an evolving myocardial infarction, but the effect of frequent ventricular ectopic beats on infarct size is unknown. To evaluate the effects of ventricular extrasystoles on infarct size, dogs anesthetized with morphine and chloralose were allocated to a control group (n=15) or to groups of dogs with ventricular bigeminy produced by programmed stimulation. A sensing circuit was used to deliver one extrastimulus after each spontaneous complex with either a short coupling interval simulating interpolated PVC's (Group 1, n=10) or a long coupling interval resulting in a compensatory pause (Group 2, n=10). Ventricular extrastimuli substantially increased heart rate in group 1 dogs, but did not alter overall rate in group 2 dogs. All dogs underwent single-stage left anterior descending coronary artery ligation, followed by a 6-hour monitoring period. Premature stimulation was begun at the time of coronary artery occlusion and continued throughout the observation period. The ratio of myocardial infarct size measured using vital staining with TTC to the region at risk of infarction was substantially larger in group 1 dogs (0.58 ± .07, $p < .01$) compared to control dogs (0.24 ± .06) or to group 2 dogs (0.32 ± .07). We conclude that frequent, closely-coupled ventricular extrasystoles can increase the size of an evolving acute myocardial infarction. This may be a consideration in evaluating the need for antiarrhythmic drug therapy in patients with acute myocardial infarction.

GREATER INFARCT EXPANSION IN A CHRONIC LEFT VENTRICULAR HYPERTROPHY MODEL: POSSIBLE MECHANISM OF INCREASED MORTALITY SEEN IN HYPERTENSIVES WITH ACUTE MYOCARDIAL INFARCTION. Shellee E. Nolan MD, Pamela Dudeck BA, John A. Mannisi MD, David E. Bush MD, Harlan F. Weisman MD. Johns Hopkins Medical Institutions, Baltimore, MD

Chronic elevation in afterload which causes left ventricular hypertrophy (LVH) increases mortality after myocardial infarction (MI). Infarct expansion, early thinning and dilatation of the infarct, also increases mortality. Whether there is a relationship between chronic afterload stress and infarct expansion is unknown. To study this, rats had aortic banding or sham operation, and after 3 weeks had sham thoracotomy or MI by left coronary ligation. Surviving rats were sacrificed 7 days later and hearts fixed in diastole for analysis.

Mortality was greater in the band/MI group with most deaths within 24 h. Banded hearts without MI had significant LVH by heart weight ($p < 0.001$). Among survivors, infarct expansion was seen in MI hearts with and without bands. However, expansion measured as cavity dilatation and infarct thinning was greater in the band/MI group:

±S.E.	Sham	Band	MI	Band/MI	P
n	13	11	26	27	
Survival	92%	100%	81%	48%	< 0.001
Cav Size (mm^3)	40±5	53±5	67±8	87±8	= 0.001
Wall Thick (mm)	2.4±.1	2.7±.2	1.7±.2	1.2±.1	< 0.001

Thus, chronic increases in afterload sufficient to produce LVH are associated with greater infarct thinning and dilatation. This increase in expansion might explain the higher infarct mortality seen in patients with hypertension and LVH.

Wednesday, March 12, 1986
10:30AM–12:00NOON, Room #268
Hypertrophy and Injury

HYPERTROPHIED MYOCARDIUM IS NOT MORE SENSITIVE TO ISCHEMIC INJURY. Ruth H. Strauss, M.D., Ellen O. Weinberg, W. Mark Vogel, Ph.D., Carl S. Apstein, M.D., F.A.C.C. Boston University School of Medicine and Boston City Hospital, Boston, MA

In hypertensive patients, left ventricular hypertrophy (LVH) is associated with increased mortality. We hypothesized that LVH due to hypertension may increase the sensitivity of myocardium to ischemia (I). We compared the effects of 10 min of I at 37°C in isolated isovolumic (balloon-in-LV) buffer-perfused hearts from 8 wks hypertensive DOC-salt rats with LVH (n=7) to normotensive control (C) (n=12) rats.

The DOC-salt treatment caused significant hypertension and LVH. For DOC-salt vs C, systolic (tail cuff) BP was increased by 75% (199±10 vs 114±6mmHg, $p < 0.001$), LV weight by 45% (1390±60 vs 960±50mg, $p < 0.001$), and LV/body weight by 62% (3.4±0.2 vs 2.1±0.1mg/gm; $p < 0.001$).

During the isolated heart perfusions, the C and LVH groups received coronary perfusion pressures of 100 and 140mmHg respectively to approximate in vivo arterial diastolic pressures; myocardial perfusion rates were equal (20±1 vs 22±2ml/min/gm for C vs LVH, p=ns) and baseline LV function was comparable to in vivo values: LV systolic pressures (at LVEDP=10mmHg) were 99±5 vs 162±8mmHg for C and LVH. After 10 min of complete I and 60 min reperfusion, recovery was 63±4 vs 67±1% of baseline developed pressure and diastolic contracture was 29±6 vs 30±11mmHg for C vs LVH (p=ns).

Conclusion: When coronary perfusion pressure is adjusted to maintain tissue perfusion rates during pre- and post-ischemia, hypertrophied myocardium is not more sensitive to ischemic injury.

REDUCTION OF MORTALITY AND MYOCARDIAL ISCHEMIA REPERFUSION INJURY WITH FRUCTOSE-1,6-DIPHOSPHATE (FDP).
Angel K. Markov, M.D., F.A.C.C., Jefferson Fletcher, M.D., Dennis Strete, M.S., Patrick H. Lehan, M.D., F.A.C.C. and Harper Hellems, M.D., F.A.C.C., University of Mississippi, Jackson, MS.

FDP is reported to have substantial therapeutic effect in myocardial infarction and shock, both in animal models and man. To verify whether FDP will have similar therapeutic effect during reperfusion, in 28 anesthetized dogs a major branch of the LCA was occluded for 2 hours and then the ischemic myocardium was reperfused. Five minutes prior to reperfusion 14 dogs received 75 mg/kg IV bolus of FDP (10%) and then 6 mg/kg/min for a total of 500 mg/kg, and 14 controls received equal amount of glucose in 0.9% NaCl. The dogs surviving 2 hours post-reperfusion were allowed to recover and 24 hours later were sacrificed and the infarct size was determined histochemically. The LVEDP at 2 hours post-reperfusion of the control dogs was 24 ± 3 mm Hg, while in the FDP group it was 13.5 ± 2.6 mm Hg ($p < 0.005$). The CO, arterial pressure and contractility were higher in the FDP group ($p < 0.01$; $p < 0.05$, and $p < 0.02$ respectively). The myocardial blood flows prior to and during occlusion were similar between the groups; however, during reperfusion they were higher in the FDP group (N.S.). Eight controls died during and after reperfusion and only one in the FDP group ($p < 0.01$) despite that both groups received the same amount of Xylocaine. The infarct size in the FDP group was 17 ± 6% of the left ventriclular mass, while in the dextrose group it was 37 ± 8% ($p < 0.01$). FDP attenuated myocardial reperfusion injury and reduced significantly mortality in the model described. The mechanism appears to be related to the positive effect of FDP on anaerobic glycolysis and its ability to reduce generation of oxygen free radicals.

SELECTIVE RETROGRADE ADMINISTRATION OF SUPEROXIDE DISMUTASE VIA THE CORONARY SINUS IMPROVES INFARCT SIZE REDUCTION. Emily Diltz, M.D., David Canvasser, DVM, Nancy Fisco, Thomas Underwood, John Nicklas, M.D. University of Michigan, Ann Arbor, Michigan.

Infarct size (IS) reduction has been demonstrated in occlusion/reperfusion animal models with left atrial (LA) infusions of superoxide dismutase (SOD) begun before ischemia. To determine if IS could also be reduced by SOD at the time of reperfusion, 3 experiments were performed randomly comparing SOD administration with albumin. IS was measured in 69 open chest anesthetized dogs following 90 min of regional ischemia produced by occlusion of the proximal LAD and 6 hrs of reperfusion. Risk mass (RM) and IS were determined after sacrifice by dual perfusion staining with trypan blue and triphenyl tetrazolium chloride. Experiment I dogs received SOD (5 mg/kg) or albumin (10 mg/kg) via the LA over 2 hr beginning 15 min prior to LAD occlusion. Experiment II dogs received SOD (10 mg/kg) or albumin (10 mg/kg) IV for 5 min beginning 1 min prior to reperfusion. Experiment III dogs received SOD (5 mg/kg) or albumin (10 mg/kg) retrograde via the great cardiac vein for 5 min beginning 1 min prior to reperfusion. Results (mean ± SD):

IS/RM%

	SOD	ALBUMIN
I (n=24)	33 ± 15	38 ± 16
II (N=21)	28 ± 11	30 ± 12
III (N=17)	25 ± 9*	41 ± 15

* difference SOD vs albumin, p <.01

Therefore, only selective retrograde administration of SOD significantly reduced IS. This suggests that selective delivery to the risk region of a high concentration of an agent capable of reducing IS is critical for successful therapy.

DOES HYDROGEN PEROXIDE GENERATED BY SUPEROXIDE DISMUTASE CONTRIBUTE TO REFLOW INJURY?
Giuseppe Ambrosio, M.D., William E. Jacobus, Ph.D. and John T. Flaherty, M.D., F.A.C.C., Johns Hopkins Medical Institutions, Baltimore, MD.
Evidence is accumulating that oxygen free radicals, particularly superoxide anions generated upon reperfusion of ischemic myocardium, may play an important role in the genesis of reflow injury. However, superoxide dismutase (SOD) catalyzed dismutation of superoxide radicals leads to the formation of hydrogen peroxide, which could potentially cause further myocardial damage. To determine whether catalase (CAT), an enzyme capable of scavenging hydrogen peroxide, is beneficial when added to treatment with SOD or whether endogenous catalase or glutathione peroxidase activities are sufficient to metabolize the hydrogen peroxide generated by SOD, 36 Langendorff perfused rabbit hearts were subjected to 30 min of normothermic (37°C) total global ischemia. At the time of reperfusion 12 hearts received 60,000 IU of recombinant human SOD (h-SOD) produced by genetic engineering, as a bolus followed by 100 IU/ml for 15 min; 12 hearts received h-SOD + 60,000 IU of CAT as a bolus followed by 100 IU/ml of both enzymes for 15 min; and 12 hearts received a bolus and 15 min of normal perfusate. All hearts then received standard perfusate for 30 additional min. Recovery of left ventricular developed pressure (DP) was measured by means of an intraventricular balloon. Phosphorus 31-NMR spectroscopy allowed continuous monitoring of myocardial ATP and phosphocreatine (PCr) content Results below are expressed as percent of baseline.

* = p < 0.05 vs Control hearts

Experimental Group	End of Ischemia ATP(%)	End of Ischemia PCr(%)	End of Reflow DP(%)	End of Reflow PCr(%)
h-SOD	32 ± 4	8 ± 2	68 ± 5*	88 ± 8*
h-SOD+CAT	29 ± 3	7 ± 1	66 ± 6*	83 ± 6*
Control	34 ± 2	7 ± 2	48 ± 4	65 ± 5

Despite equal depletion of ATP and PCr by the end of the ischemic period, recovery of ventricular function and PCr content was equally improved in h-SOD and h-SOD+CAT treated hearts compared to Control. Thus, h-SOD administration resulted in significant reduction in reflow injury. CAT provided no additional benefit, suggesting either that the hydrogen peroxide generated by SOD is not harmful or that endogenous mechanisms are capable of scavenging the quantities of hydrogen peroxide generated by the dismutation reaction.

BENEFICIAL LONG TERM EFFECT OF INTRACORONARY PERFLUOROCHEMICAL ON INFARCT SIZE AND VENTRICULAR FUNCTION IN A CANINE REPERFUSION MODEL.
Mervyn B. Forman, M.D., B. Hadley Wilson, M.D., David Puett, B.A., Donna Bostick, R.N., Gottlieb C. Friesinger, M.D., F.A.C.C., Renu Virmani, M.D. Vanderbilt University, Nashville, Tennessee.
The long term effect of low dose intracoronary (IC) perfluorochemical (PFC), Fluosol-DA, on infarct size reduction, ventricular function and infarct evolution was studied in 17 anesthetized closed-chest dogs. After 90 minutes of proximal LAD occlusion the animals were reperfused with IC streptokinase, ventilated with 100% oxygen and randomized into two treatment groups (Gp): GpI (n=9) received oxygenated saline and GpII (n=8) oxygenated PFC IC at 15 ml/kg. Heart rate, systolic pressure, LV filling pressure and contrast ventriculograms were obtained at baseline, occlusion, 3, 24 hours, 1 and 2 weeks post reperfusion. 24 hr Holter monitoring was performed 12 days post reperfusion. Regional LV function was analyzed using a computerized radial shortening method. Area at risk (A_R) was defined in vivo using Monastryl blue and area of necrosis (A_N) with modified trichrome stain. No significant differences were noted in hemodynamic parameters. Results are expressed as mean ± SEM,*p<0.001, **p<0.01.

	A_N/A_R (%)	A_N/LV (%)	A_R/LV (%)	ΔRS^+ (%)	PVC/hr
GpI	36.4±2.9	14.4±2.0	33.2±6.6	8.3±2.6	2.9±2.8
GpII	*12.8±3.3	*5.1±1.8	34.6±3.5	**25.4±5.3	18.4±17.7

\+ change in radial shortening (RS) 3 hrs vs 2 weeks.
There was no significant difference in infarct morphology at 2 weeks between the two groups. IC PFC markedly reduces infarct size in the canine reperfusion model without increasing propensity for ventricular arrhythmias. IC PFC also resulted in significant improvement in regional LV function in the ischemic zone.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 10:00AM–11:00AM
Hall D, Georgia World Congress Center
Valvular Disease

"DOPPLER DISEASE": FOUR VALVE INSUFFICIENCY IS COMMON THOUGH OFTEN CLINICALLY INSIGNIFICANT.
Richard S. Meltzer, M.D., F.A.C.C., Laura Abovich, B.S., Mindy Finkelstein, B.S. Mt. Sinai Medical Center, New York, NY

During a 7 month period in 1984-5, 30 patients were identified with regurgitation of all 4 cardiac valves by Doppler echocardiography (2029 had echoes, including 1115 Doppler studies during this time). Valvular insufficiency was diagnosed with the Doppler sample volume positioned just proximal to the relevant valve; holosystolic turbulence was necessary to diagnose mitral or tricuspid regurgitation, and early and mid-diastolic turbulence was required for semilunar regurgitation. Of the 30 patients with regurgitation of all 4 valves, there were 7 men and 23 women, aged 43-86 (mean 69) years. Only 21 of them had holosystolic murmurs and only 9 had early diastolic murmurs of valvular regurgitation. Left heart failure was clinically present in 24 and right heart failure in 17. In only 4 was valvular regurgitation (2 aortic, 2 mitral) felt to be the primary problem leading to heart failure. Echo measurements (mean ± 1 SD): LA: 51 ± 11 mm; LV (end diastole): 53 ± 11 mm; fractional shortening 31 ± 10%. It is concluded that insufficiency of all 4 cardiac valves is common by Doppler echocardiography, usually in the setting of biventricular failure, though as a group LV dimension and fractional shortening was normal. There may be a female predominance. Though a mitral or tricuspid insufficiency murmur is likely to be present, a semilunar valve insufficient murmur is usually not detected despite careful auscultation by a cardiologist. Physicians need to be aware of the frequency of valvular insufficiency by Doppler echocardiographic techniques and to realize that not all "Doppler disease" is clinical disease.

ABNORMAL PLASMA LEVELS OF ATRIAL NATRIURETIC FACTOR (ANF) IN PATIENTS WITH SYMPTOMATIC MITRAL VALVE PROLAPSE André Pasternac, M.D., F.A.C.C. Simon Kouz, M.D., Jolanta Gutkowska, Ph.D., Robert Petitclerc, M.D., Bruno Vellas, M.D., Jacques de Champlain, M.D., Ph.D., Marc Cantin, M.D., Ph.D., and Martial G. Bourassa, M.D., F.A.C.C., Montreal Heart Institute and University of Montreal, Montreal, Canada.

Volume depletion sensitivity, postural hypotension and increased adrenergic activity have suggested an abnormality in plasma volume control in patients (pts) with mitral valve prolapse (MVP). To test whether an abnormality in atrial natriuretic factor (ANF) was present, we studied 15 pts (12 females, 3 males, mean age 47.1± 3.7 yrs) with MVP (M and 2 D Echo). Blood pressure, heart rate and free plasma norepinephrine (NE), epinephrine and dopamine (Peuler and Johnson technique) were obtained in supine (s) and standing (st) positions. Plasma ANF was measured by radio-immunoassay, 32 males and 29 females provided ANF control values (males: 59.6±3.9 (SE) pg/ml; female 79.3±4.4 pg/ml). Patients were divided into 3 groups: I: low, II: normal and III: high values of ANF

	I		II		III
# pts	8		3		4
Age (yrs)	48.4±4.6	NS	54.3±12.7	NS	39.0±5.6
M/F	2/6		0/3		1/3
ANF (pg/ml)	39.9±3.2	p<0.001	68.1±2.6	p<0.05	162.0±32.0
NEs (pg/ml)	300±17	NS	318±108	NS	258±82
NEst (pg/ml)	663±51	NS	802±288	NS	557±182

ANF was decreased in 8/15 patients (53.3%) and increased in 4/15 (26.6%). The levels of ANF showed no relationship to age, blood pressure, heart rate and catecholamines. NE levels were elevated in all 3 groups in s and st positions (p<0.01 with control values), but epinephrine and dopamine levels were normal in s and st positions in all groups.

These data suggest that symptoms in patients with MVP reflect variable hemodynamic and neuroendocrine responses to altered adrenergic and plasma volume control.

A NEW METHOD FOR CALCULATING VALVE AREA IN MITRAL STENOSIS. William E. Lawson, M.D., Marcis T.Sodums, M.D., Claire Proctor, RDMS, Peter F. Cohn, M.D., F.A.C.C. SUNY Health Sciences Center, Stony Brook, NY.

Use of the Gorlin formula for predicting mitral valve area (MVA) in mitral stenosis is time consuming, requiring planimetry for estimation of the mean transmitral gradient, and often limited by the ability to obtain an accurate cardiac output. The doppler pressure 1/2 time formula for mitral stenosis is relatively insensitive to changes in cardiac output and has been shown to provide an accurate estimation of MVA. Applying this formula to cath data allows quick and accurate calculation of the MVA from 4 variables: the initial and end diastolic (D) wedge (PCW) pressures (P_o,P_1), the left ventricular end diastolic pressure (LVEDP), the diastolic filling period (DFP-in milliseconds (mS)).

$$MVA\ (cm^2) = \left[\frac{733}{DFP}\right] \left[1 - \sqrt{\frac{P_1 - LVEDP}{P_o}}\right]$$

Since the exponential decline in D transmitral gradient is altered by atrial systole, in patients in sinus rhythm the pre "a" values of PCW, LVEDP, and DFP should be used in the calculation of MVA. A group of 11 patients with mitral stenosis(.57-1.94cm^2) had their MVA calculated using both methods.Both formulas consistently yielded similar results (correlation coefficient r=.98). The new method offers the advantage of not requiring cardiac output to be measured or planimetry of the valve gradient. In atrial fibrillation the new method yields a good estimate of the MVA from individual cycles. Under conditions where D diastasis occurs (such as mild mitral stenosis and during long cardiac cycles) the formula simplifies to the easily calculated:

$$MVA\ (cm^2) = \frac{733}{DFPD} \qquad (DFPD = DFP \text{ to diastasis in mS})$$

WHY DO INTRAVENOUS DRUG ABUSERS DEVELOP TRICUSPID VALVE ENDOCARDITIS? Martin E. Goldman MD FACC, Robert Reichstein MD FACC, Michael Borodkin, Karen Stavile RN, Stephen Winters MD, Valentin Fuster MD FACC, Mt. Sinai Medical Center, NY,

Usually, underlying valve pathology predisposes patients (pts) to endocarditis. Intravenous drug abusers (Addicts) have a much greater incidence of tricuspid valve (TV) endocarditis than normal pts. Since TV prolapse is probably the most common abnorality of the TV, present in up to 52% of pts with mitral valve prolapse (MVP), we evaluated 28 consecutive addicts with TV endocarditis to determine if they had a higher incidence of MVP and therefore possible TV abnormalities. Over a 3 year period there were 20 males and 8 female addicts aged 32±7 years, all with clinical TV endocarditis and confirmed with positive TV vegetations documented by two-dimensional echocardiography (2DE). Since the TV was already abnormal due to endocarditis and could not be analyzed for native abnormalities, M-mode and 2-dimensional echocardiograms were read blindly by 2 reviewers for possible MVP or mitral valve redundancy (3 or more systolic C-D lines).

Interestingly, 17 of 28 pts (61%) with TV endocarditis had MVP and 26 of 28 (93%) had either MVP or redundant mitral valves. Additionally, the tricuspid vegetation occurred on the atrial side rather than the ventricular side of the TV in 24/28 (86%) pts suggesting underlying TV regurgitation. Also, the vegetation appeared on the anterior leaflet of the TV, the largest of the 3 leaflets, and possibly with the most myxomatous degeneration, in 24/28 pts.

Thus, despite the large number of intravenous drug abusers in the country, only a small percentage develop tricuspid valve endocarditis. These patients may have underlying myxomatous tricuspid valve disease with tricuspid regurgitation as their predisposing factor to endocarditis.

EFFECT OF NITROGLYCERIN DURING HEMODYNAMIC ESTIMATION OF VALVE ORIFICE IN PATIENTS WITH MITRAL STENOSIS Jonathan L. Halperin, M.D., F.A.C.C., Elizabeth B. Rothlauf, R.N., Bruce P. Mindich, M.D., F.A.C.C., Kenneth M. Brooks, M.D., F.A.C.C., and John A. Ambrose, M.D., F.A.C.C., Mount Sinai Medical Center, New York, NY.

In mitral stenosis (MS), valve (MV) orifice (MVA) calculations using pulmonary (P) capillary wedge pressure (PW) as a substitute for left atrial pressure (LA) may overestimate the severity of disease. Previous studies have shown that prosthetic MVA determined from trans-septal LA pressure exceeds area derived from PW measurement due to P venoconstriction (vnc), which is reversed by nitroglycerin (TNG). To assess the effect of TNG, 0.6 mg sublingual, we studied 20 (pts) with MV disease during preoperative catheterization using PW. Data are mean ± SEM; F = flow; G = gradient.

	CONTROL	TNG	P
MVG (mean; mmHg)	12.6 ± 1.2	11.5 ± 1.0	NS
MVF (liters/min)	4.0 ± 0.3	4.1 ± 0.3	NS
MVA (Gorlin; cm^2)	0.8 ± 0.1	1.1 ± 0.2	<0.05

12 pts had MS without regurgitation and, in these, MVA calculated after TNG was 0.4 ± 0.1 cm^2 larger than control. Administration of TNG during evaluation of MS eliminates P vnc which raises PW above LA in some pts. TNG may add diagnostic accuracy without trans-septal catheterization. Whether the response to TNG has direct therapeutic value in MS has yet to be determined.

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February 1986 170A

BENEFICIAL EFFECTS OF NITRATE THERAPY ON LEFT VENTRICULAR HEMODYNAMICS AND FUNCTION IN PATIENTS WITH CHRONIC SEVERE MITRAL REGURGITATION

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Decrease of LV volume & mitral regurgitant orifice has been suggested as a potential mechanism of reduction(↓)of mitral regurgitation(MR). Nitrates exert a predominant venodilatory effect & may lead to ↓ of venous return & LV volume. We assessed the hemodynamic effects of intravenous nitroglycerin(NTG)titrated to ↓ mean pulmonary artery wedge pressure(PAW) ≥30% in 13 patients (pts) with chronic severe MR. Heart rate(HR) mean blood pressure (MBP), right atrial pressure(RA), cardiac index(CI), forward stroke volume index(FSVI) systemic vascular resistance(SVR), LV end diastolic volume(EDV), LV end systolic volume(ESV), LV ejection fraction(EF), regurgitant fraction(RF) & volume(RV) were evaluated at baseline(C) & during NTG infusion. * P<0.05 vs C.

	HR (beats/min)	MBP (mmHg)	RA (mmHg)	CI (L/min/m^2)	PAW (mmHg)	SVR (dynes·s·cm^{-5})
C	95±20*	92±11*	12±5*	2.0±0.6	23±6*	1986±524*
NTG	89±18	79±12	7±4	2.2±0.5	14±6	1576±557

	EDV (ml)	ESV (ml)	EF (%)	FSVI (ml)	RF (%)	RV (ml)
C	248±54*	132±61*	48±16*	22±8	67±15	80±34
NTG	214±53	97±44	56±16	26±7	64±9	73±32

Summary - NTG resulted in a significant ↓ in LV preload & afterload leading to ↓ on LV volumes & improvement of EF. However, there was no change in RF or RV.

Conclusions: Nitrate therapy exerts beneficial effects on LV hemodynamics & function in pts with severe MR. 2) As RV & RF do not change these effects are due to peripheral vasodilation effects & not due to improvement of MR.

FAILURE OF LEFT ATRIAL SIZE TO PREDICT SYSTEMIC EMBOLISM IN PATIENTS UNDERGOING VALVE REPLACEMENT.

Cecil M. Burchfiel, Ph.D., Heidi Krause-Steinrauf, B.S., Karl E. Hammermeister, M.D., FACC, Michael H. Crawford, M.D., FACC, Gulshan K. Sethi, M.D., Participants in VA Cooperative Study on Valvular Heart Disease.

To determine whether left atrial dimension (LAD) measured by M-mode echocardiography was associated with systemic embolism (SE) following valve replacement (VR), we compared baseline characteristics and LAD between 39 patients with SE and 487 without SE from the VA Cooperative Study on Valvular Heart Disease. Data were collected prospectively; average followup after VR was five years. The average annual incidence rate of SE was 0.5% following aortic VR (8/338), 2.9% following mitral VR (20/140), and 2.9% following multiple VR (7/48). SE occurred more frequently in patients with nonsinus than sinus rhythm (12.4% vs. 6.2%, p<.05), and in patients with a prior history of SE (15.2% vs. 6.7%, p<.05), while mean pulmonary artery pressure was significantly higher in patients with SE than in those without SE (47 vs. 41 mmHg, p<0.05). However, mean LAD was not significantly different when patients with SE were compared to those without SE (4.98 vs. 4.62 cm, p>0.10). LV ejection fraction was slightly higher in patients with SE than in those without (0.54 vs. 0.49, p=0.10). Other variables which were not significantly associated with SE were functional class, LA enlargement on chest x-ray or ECG, smoking habits, anticoagulant use, systolic shortening fraction, LV end-diastolic dimension, and CI. We conclude that history of prior SE, valve(s) replaced, nonsinus rhythm and increased pulmonary artery pressure, but not left atrial enlargement by any criteria, identify patients at increased risk for SE after VR.

CLINICAL-MORPHOLOGIC CORRELATION IN 31 PATIENTS WITH MITRAL STENOSIS AND PURE TRICUSPID REGURGITATION: ANULAR CIRCUMFERENCE IS USEFUL IN PREDICTING WHICH TRICUSPID VALVES NEED REPLACEMENT OR REPAIR AT THE TIME OF MITRAL VALVE SURGERY FOR MITRAL STENOSIS

Bruce F. Waller, M.D.,F.A.C.C., Yousuf Mahomed, M.D..F.A.C.C., John W. Brown, M.D.,F.A.C.C., John E. Pless,M.D. Indiana University Medical Center, Indianapolis.

Preoperative clues to tricuspid valve (TV) morphology useful in management of pure tricuspid regurgitation (TR) at the time of mitral valve stenosis (MS) replacement (MVR) or repair is lacking. Thus, purely regurgitant TVs from 31 patients (pts) with MS were examined: 17 operatively-excised TVs and 14 necropsy-excised TVs. Of the 31 TVs, 14 (45%) were morphologically classified as rheumatic TR and 17 (55%) as "functional" TR (normal leaflets and commissures). TV anular circumference was a useful separator of the 2 types of TVs: rheumatic valves had normal anuli (10.5-12.0 cm, m=11.4)(normal TVs 9.0-12.5 cm, m=11.0) while the "functional" TR valves had markedly dilated anuli (12.5-14.5 cm, m=13.6), p<.05. Thus, measurement of TV anular circumference is a useful predictor of the morphologic status of purely regurgitant TV in the presence of MS and may aid in therapeutic decisions regarding TV replacement or repair.

RISK OF ANTICOAGULATION IN PREGNANT WOMEN WITH ARTIFICIAL HEART VALVES.

IGNACIO ITURBE M.D, CARMEN FONSECA,M.D., ALEJANDRO ZAJARIAS M.D., OSVALDO MUTCHINIK M.D., ANGEL SANTOS M.D., EDUARDO SALAZAR M.D, F.A.C.C. Instituto Nacional de Cardiología "Ignacio Chavez" Mexico City, Mexico.

The use of anticoagulants during pregnancy in patients with artificial heart valves represents a serious therapeutic dilemma. In this prospective study we followed 64 pregnancies(PR) in 53 patients(P). They were divided in 3 groups according to the time of diagnosis of PR. All were taking acenocoumarol(AC) at the time of diagnosis. Group I received 5000U of heparin(H) sc q12h from the 6th to the 12th of PR (20PR). Group II: The P were switched to H after the 7th week until the 12th week (12PR). After the 12th week the 2 groups received AC. Group III received AC during the whole PR (32PR).

The rate of abortions was 15.6% for the 2 groups that received H and 18.7% for the group that received AC during the whole PR. 49 out of 51 children were examined, 2 out of 26 from group III had classical signs of warfarin embryopathy(WE), and 5 more of group III and 2 of group II had abnormalities of the facial bones suggestive of WE. Two P of group I had valve thrombosis while receiving H and one died. Both had Björk-Shiley mitral prostheses. It is concluded that the risk of WE is high if AC is administered during the first trimester of PR. H administered sc at a fixed dose has a higher risk of thrombotic events than AC. The risk of WE increases if AC is switched to H after the 7th week compared to the ones that received it before the 7th week. There is a need to evaluate the use of higher doses of H to minimize the risk of thrombosis to the mother.

PROSTHETIC HEART VALVES AND PREGNANCY: MATERNAL AND INFANT OUTCOME. John H. McAnulty MD, Neil Blair, Charles Walance, Kent Ueland MD. Oregon Health Sciences University, Portland, Oregon and Stanford University, Palo Alto, CA.

To determine maternal and infant outcome in pregnancy in women with prosthetic valves (V) we evaluted 195 patients (age 15-35), 82 with tissue (TV) and 113 with mechanical (MV). Prior to receiving the valve, 54 women had been sterilized. Of 141 patients capable of pregnancy, 24 were lost to follow-up or died with valve replacement. In the remaining 117 patients, 12 were eventually sterilized.

35 of 117 women (30%) had 53 pregnencies. Women with TV off anti-coagulants had 74% incidence of live birth, while those with MV on anti-coagulants had a 27% incidence of live birth ($p<.05$). Spontaneous abortions (32% overall) and therapeutic abortions (11% overall) were greater in women with MV. Maternal complications occurred in 47% overall and included emboli (6%), hemorrhage (13%), congestive heart failure (15%), and death (2%). Women with TV had a greater percentage of heart failure, while other complications occurred more often in those with MV. In the 25 living offspring, no obvious congenital abnormalities were detected: 9 were the result of women on warfarin derivatives.

The incidence of maternal complication is high but not clearly above that in nonpregnant women with prosthetic valves. The incidence of spontaneous and therapeutic abortions is high, and more common in MV. The live-born offspring had no major abnormalities.

SPONTANEOUS COURSE OF AORTIC VALVE DISEASE.

Juraj Turina, M.D., Otto Hess, M.D., Flavio Sepulcri, M.D., Hans P. Krayenbuehl, M.D., Medical Policlinic, University Hospital, Zurich, Switzerland.

188 patients (pts), age 16 to 72 years (y), with aortic valve disease of various degree were followed up to 20 y after initial heart catheterization. Evaluated were also pts which declined surgery or died before recommended operation. During the follow-up 41 pts died and 85 underwent valve replacement. Cardiac death and valve surgery were the end-points for calculation of the event-free survival. According to hemodynamic data initial aortic valve disease was severe in 79 pts, moderate in 81 and mild in 28 pts. Aortic stenosis (AS) was present in 76, aortic regurgitation (AR) in 84 and combined lesion (AS/AR) in 28 pts. Event-free 5 and 10 y survival was 55% and 25% in AS and 67% and 25% in AR. Event-free 2 and 5 y survival was decreased in pts with severe disease (50% and 32% in AS, 86% and 55% in AR, 38% and 38% in AS/AR), severely symptomatic (NYHA class III and IV) pts (31% and 22% in AS, 57% and 29% in AR, 29% and 29% in AS/AR), pts with history of heart failure (29% and 0% in AS) and syncope (40% and 29% in AS). In severe AS 61% of pts were also severely symptomatic or had a syncope whereas in severe AR only 17% of pts had the same signs. Event- free 2 y survival of asymptomatic or oligosymptomatic (NYHA class I and II) pts was 100% in severe AS and 96% in severe AR. Pts with mild aortic valve disease had an 100% event-free 5 y survival. We concluded that 1) severe hemodynamic and symptomatic aortic valve disease requires immediate valve surgery, 2) in asymptomatic and oligosymptomatic pts with severe aortic stenosis surgery can be postponed until symptoms increase, 3) in severe aortic regurgitation indication for surgery should not rely only on symptoms and 4) mild aortic valve disease does not require observation within the first 5 y after diagnosis.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 10:00AM–11:00AM
Hall D, Georgia World Congress Center
Valvular Disease

COMPARISON OF MODELS TO EVALUATE DIASTOLIC PRESSURE VOLUME RELATIONSHIP IN AORTIC VALVE DISEASE

Tomoyuki Murakami, MD, Otto M. Hess, MD, Hans P. Krayenbuehl, MD. University Hospital, CH-Zurich

Several mathematical models are currently used to evaluate the diastolic pressure(P)-volume(V) relationship. Three different models [1) simple elastic: $P=\alpha_1 e^{\beta 1 V}$; 2) viscoelastic: $P=\alpha_2 e^{\beta 2 V}+\eta_2 dV/dt$; 3) simple elastic with asymptote: $P=\alpha_3 e^{\beta 3 V}+C_3$] were tested in 24 pateints with aortic stenosis(AS), 20 with aortic insufficiency(AI) and 6 controls(C). P-V relations were obtained from biplane angios and micromanometry. The constant of chamber stiffness($\beta_1, \beta_2, \beta_3$) was determined from the linear relation between lnP, $\ln(P-\eta_2 dV/dt)$ or $\ln(P-C_3)$ and V using an iteration procedure and the correlation coefficient(r) was obtained. Normalization of P-V relation was performed by defining a reference V as the V at P, $P-\eta_2 dV/dt$ or $P-C_3=1$ mmHg(V1). With this definition, the constant of the P-normalized V[(V-V1)/V1] relation can be expressed as $-\ln\alpha_1$, $-\ln\alpha_2$ and $-\ln\alpha_3$ in each model.

	model 1			model 2			model 3		
	r	β_1	$-\ln\alpha_1$	r	β_2	$-\ln\alpha_2$	r	β_3	$-\ln\alpha_3$
C	.97	.034	.65	.98	.035	.79	.98	.049	2.31
AS	.93	.024	.09	.95★	.029	.70	.97★§	.063○	5.94
AI	.91	.023	1.04	.95★	.025	2.75	.96★	.041○	6.88

★ P<.05 vs model 1; § P<.05 vs model 2; ○ P<.05

Conclusions: 1) models with an asymptote are required to evaluate P-V relationship; 2) in the non volume-normalized model 3, an increased chamber stiffness(β_3) is observed in AS as compared to AI; 3) the similar stiffness parameters ($-\ln\alpha_3$) obtained in AS and AI by the volume-normalized model 3 is in keeping with a similar myocardial stiffness found in AS and AI evaluated by the stress-strain relationship.

THE INFLUENCE OF CORONARY ARTERY DISEASE ON THE HEMODYNAMIC PROFILE OF PATIENTS WITH ANGINA AND AORTIC STENOSIS

Mark Lipton, M.D., James Slater, M.D., Paul Kramer, M.D., William Schwartz, M.D., Howard Winer, M.D., F.A.C.C., Itzhak Kronzon, M.D., F.A.C.C., Ephraim Glassman, M.D., F.A.C.C. New York Univeristy Medical Center, New York, NY

To determine whether patients with aortic stenosis (AS) and coronary artery disease (CAD) develop angina with milder AS than patients without CAD, we reviewed the non-invasive and invasive data from 77 consecutive adult patients with angina and significant AS (valve area index <0.75 cm/M^2 or peak gradient >40mmHg). LV angiography provided a score of LV dysfunction (higher scores denote more abnormality). Patients with significant CAD (>70% stenosis) differed from patients with CAD (means ± SEM):

	AS+CAD (N=50)	AS, no CAD (N=27)	P
Age	70±3±1.1	68.4±2.2	NS
Male sex	72.0%	48.1%	<0.05
Valve area	0.81±0.05	0.57±0.04	<0.001
Mean Gradient	48.2±3.7	71.8±6.1	<0.001
Cardiac index	2.84±0.08	2.70±0.11	NS
LV score	4.8±0.9	1.3±0.9	<0.02

When age, sex, and LV function were controlled by multivariate analysis, CAD remained a highly significant predictor of AS severity. The degree of CAD was negatively correlated with the severity of AS ($R=-0.47$, $p<0.001$). EKG and echocardiographic parameters did not differentiate the two groups. The additive effects of valvular and coronary artery stenoses on myocardial O_2 supply-demand ratio result in angina with less severe AS.

RESPONSE TO SUBMAXIMAL AND MAXIMAL EXERCISE IN AORTIC INSUFFICIENCY. Richard A. Wilson, MD, Barry H. Greenberg, MD, FACC, Barry Massie, MD, FACC, J. David Bristow, MD, FACC, Melvin Cheitlin, MD, FACC, Debra Loge, CNMT, David Broudy, MD, G. Krishnamurthy, MD, David Thomas, PhD. Oregon Health Sciences University, Portland, Oregon.

To evaluate whether changes in cardiac performance occurred in a stepwise manner during exercise (ex) in aortic insufficiency (AI) we studied 60 asymptomatic patients (pts) during graded supine bicycle ex. All had LV dilatation and preserved resting ejection fraction (EF).

Measurements of heart rate (HR), systolic blood pressure (SBP), end-diastolic volume index (EDVI), end-systolic volume index (ESVI), EF and SBP/ESVI were obtained serially at rest, at the midpoint of ex (i.e.: submax) and at peak ex (MAX):

	kpm/min	HR	SBP mmHg	$EDVI_2$ cc/m^2	$ESVI_2$ cc/m^2	EF	$SBP/ESVI_2$ mmHg/cc/m^2
Rest	-	65	140	159	56	.60	2.9
SUBMAX	383	101*	170*	147*	53	.64	4.2*
MAX	673	128+°	200+°	135+°	48+°	.65	6.1+°

p<0.05 *Rest vs SUBMAX, +Rest vs MAX, ° SUBMAX vs MAX

Patients were divided into three grps: GrpI ↑ >.05 EF, GrpII ≤.05 change in ER, and GrpIII ↓ >.05 EF. In all 3 grps HR, SBP increased and EDVI decreased in a stepwise progressive manner from rest to submax to max ex. In GrpI EF increased and in GrpIII EF decreased in a progressive stepwise fashion. SBP/ESVI increased 4% at submax and 29% at peak in GrpIII: these changes were significantly less than the 83% and 200% changes seen in GrpI.

We conclude that in this grp of AI pts: 1) stepwise changes in LV volume and EF occur with supine ex, and 2) these stepwise changes occur regardless of EF response to ex.

WHAT DOES EXERCISE RADIONUCLIDE ANGIOGRAPHY ADD TO THE REST STUDY IN THE PREOPERATIVE EVALUATION OF SEVERE AORTIC REGURGITATION?
D. Douglas Miller, M.D., John B. Gill, M.D., Judith H. Murphy, M.D., Adolph M. Hutter, Jr., M.D., F.A.C.C., David J. Kanarek, M.D., Charles A. Boucher, M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA

To determine the additional diagnostic utility of exercise (ex) radionuclide angiography (RNA) compared to rest RNA in evaluating severe isolated aortic regurgitation (AR), 53 such patients underwent pulmonary ex gas exchange analysis and ex first pass RNA, 22 of whom subsequently underwent valve replacement (AVR). When classified by rest ejection fraction (EF), 17 had EF ≥.50, 19 had EF=.41-.49 and 17 had EF ≤.40. Significant correlations with a higher rest EF ($p \leq 0.05$) included: lower rest end-diastolic volume (342±91 vs 402±86 vs 538±150ml, mean±1SD), lower rest end-systolic volume (154±44 vs 217±48 vs 352±115ml), lower ex systolic BP (136±23 vs 145±30 vs 159±33torr) and higher oxygen uptake at anaerobic threshold (23±7 vs 18±7 vs 16±5ml/kg/min) and peak ex (29±7 vs 25±7 vs 22±7ml/kg/min). These 3 AR subgroups did not differ in age or severity of AR measured by LV/RV stroke counts ratio. The rest EF also predicted the change in EF from rest to ex (+.05±.06, +.02±.08, -.04±.06, respectively, p<.01). AVR was performed in 1(6%), 7(38%), and 13(76%) of the 3 rest EF groups, respectively (p<.001). Stepwise logistic regression analysis showed that rest EF was the only clinical, exercise or radionuclide parameter that correlated with undergoing AVR (p<0.001).

We conclude: first pass rest RNA data alone separates severe AR pts into functional subgroups. When rest LVEF is ≥.50, EF rises with ex and when rest EF is ≤.40, EF falls with ex. Only in the mid range of EF, .41-.49, does the ex RNA add information to the rest study, because the ex EF response in this setting is variable.

THE RESTING ELECTROCARDIOGRAM IN AORTIC REGURGITATION
Mary J Roman, MD, Paul Kligfield, MD, FACC, Richard B Devereux, MD, FACC, Nathaniel Niles, MD, Clare Hochreiter, MD, Jeffrey S Borer, MD, FACC. Cornell Medical Center, New York, NY

To test the hypothesis that the "strain" pattern of repolarization (StR) on the electrocardiogram (ECG) is associated with structural and functional changes of potential prognostic value in patients (pts) with aortic regurgitation (AR), we compared ECG findings with echocardiographic and radionuclide findings in 95 pts with pure chronic AR. Both left ventricular (LV) mass and LV end-systolic stress (ESS) were independently related to StR by logistic regression analysis. Moreover, in contrast to 54 pts with normal repolarization (NR), 41 pts with StR had greater LV end-systolic dimension (5.2 ± 1.2 vs 4.4 ± 0.7 cm, p<.001), greater LV end-diastolic dimension (7.2 ± 1.1 vs 6.6 ± 0.8 cm, p<.002), greater LV mass (431 ± 138 vs 303 ± 89 gm, p<.001), higher LV ESS (128 ± 46 vs 95 ± 27 dynes/cm^2 x10^3, p<.001), lower LV fractional shortening (FS) (28 ± 8 vs 34 ± 5%, p<.001), lower resting LV ejection fraction (EF) (45 ± 12 vs 51 ± 7%, p<.02), and lower exercise LVEF (39 ± 11 vs 51 ± 8%, p<.001). Among the 72 asymptomatic (asx) pts, those with NR had significantly lower prevalences of FS <25% (1/45 vs 5/27), LV systolic dimension >5.5cm (1/45 vs 8/27), and exercise LVEF <40% (2/39 vs 10/24, p<.05 for each comparison). During a 28 month follow-up period, valve replacement occurred in only 1/37 initially asx pts with persistently NR but in 10/25 initially asx pts who exhibited or developed StR (p<.006). We conclude that StR in AR is associated with markedly increased LV ESS and LV mass, that asx AR pts with StR have a higher risk of LV dilatation and dysfunction than asx pts with NR, and that asx pts with NR have a low likelihood of severe LV functional and geometric abnormalities.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 9:00AM–10:00AM
Hall D, Georgia World Congress Center
Cardiovascular X-Ray/NMR/CT/PET

GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION IN ISCHEMIC HEART DISEASE: ACCURATE EVALUATION BY CINE-CT
TM Bateman, MD, FACC; GT O'Byrne, MD; JS Forrester, MD, FACC; JS Whiting, PhD; AL Aronson, MD; SV Schauer, MS; DS Berman, MD, FACC; HJC Swan, MD, PhD, FACC. Cedars-Sinai Medical Center, Los Angeles, California.

Eight level rapid-acquisition cardiac cine-computed tomography (Cine-CT) was performed in 23 post-CABG pts within 2 wks of 3-view radionuclide ventriculography (RNV). Acquisition was ECG-gated (10 images/level, at 58 msec increments from the R wave) following peripheral IV injection of 30-45 ml of renografin-76 in the modified short axis projection. Ejection fraction (LVEF) was calculated using the summed end-diastolic and end-systolic tomographic slices. Six myocardial regions (anteroseptal, anterolat, post-lat, post-basal, inf, septal) were scored by different, blinded observers for RNV and Cine-CT images as follows: -1=dyskinesis, 0=akinesis, 1 or 2=mod or mild hypokinesis, 3=normal. LVEF by Cine-CT (53±19%; range 21-76%) did not differ from that by RNV (50±18%; range 18-73%), and the regression slope (1.02) and y-intercept (2.2) were not different from the line of identity (r=0.92; p=0.22). Eight pts with transmural MI were correctly identified on Cine-CT by both akinetic/dyskinetic segments and by systolic myocardial thinning. Of 138 regions for potential evaluation, 25 (18%) could not be scored by RNV vs only 3 (2%) by Cine-CT. Thirteen of the unscored regions by RNV were "paradoxic" septae; 7 were normal by Cine-CT and 6 were hypo or akinetic. Of the remaining 110 segments, there was agreement (normal vs abnormal) in 103 (94%) of readings. RNV detected 42 abnormal segments, while Cine-CT detected 47. Wall motion scores differed by >1 in only 18% of concordantly detected abnormal walls. Hence, Cine-CT accurately evaluates global LV function, may be superior to RNV for assessing regional function, and provides data about postoperative septal function not available by RNV.

QUANTITATION OF LEFT VENTRICULAR MASS AND VOLUMES IN NORMAL PATIENTS USING CINE COMPUTED TOMOGRAPHY

John A. Rumberger, Ph.D., M.D., Andrew J. Feiring, M.D., Michael R. Rees, M.D., Stephen R. Ell, Ph.D., M.D., and Melvin L. Marcus, M.D., F.A.C.C., University of Iowa and CV Center, Iowa City, Iowa

In a majority of patients none of the currently employed cardiac imaging modalities (contrast ventriculography, echocardiography or nuclear angiography) has been shown to accurately determine left ventricular (LV) mass (M), cavity volumes (V) and global ejection fraction. Cine computed tomography (CT) is a minimally invasive technique which possess high temporal (up to 17 frames/sec) and spatial resolution. This technique can be applied to evaluate cardiac hypertrophy and dynamics in a broad spectrum of patients. However, before such abnormalities can be defined in patients the normal ranges of LVM and LVV must be established for cine-CT. To accomplish this, we obtained cine short axis tomograms from apex to base in 14 normal subjects (ages 21-36 years) during contrast infusion (range 8 to 10 tomograms per subject). LVM, V, stroke volume (SV) and EF were calculated from end-diastolic (ED) and end-systolic (ES) frames using Simpson's reconstruction. Results shown are mean ± S.D. (* = per body surface area). Mean arterial pressure and average heart rate were 93±10 mmHg and 72±11/min.

LVM* (gms)	LV-EDV* (cc)	LV-ESV* (cc)	LV-SV* (cc)	LV-EF (%)
97±14	72±13	23±7	50±9	69±7

LVM at ES and ED were not significantly different. This study defines the normal range of LVM and LVV in normal, adults employing cine-CT and demonstrates the feasibility of obtaining high quality apex to base cardiac short axis tomograms in patients.

SERIAL CHANGES IN MYOCARDIAL NMR T1 AND T2 VALUES WITH AND WITHOUT REPERFUSION.

Gerald Wisenberg, M.D., Frank S. Prato, Ph.D., Edwin S. Carroll, M.D., Katherine L. Turner, M.D., St. Joseph's Hospital and University of Western Ontario, London, Ontario.

To characterize changes in vivo in ischemic myocardium, 10 dogs were studied by NMR on a 0.15T system a) during 2 hours of coronary occlusion b) immediately following release of the occlusive snare c) 4 days and d) 21 days after coronary occlusion. Coronary flow and, thus, adequacy of reperfusion was monitored by microspheres. Extent of infarction was determined by histological examination. Results were as follows:

T1 AND T2 VALUES (MSEC)

	Reperfusion (n=7)		Non-reperfusion (n=3)	
	T1	T2	T1	T2
Occlusion	445±32*	52±5*	450±50*	50±8*
Release	555±65**	65±8**	455±47*	58±9*
Dog 5	512±55*	39±8	491±61**	63±8**
Dog 21	450±47*	35±7	425±41*	54±9*
Control	350±11	40±2	350±11	40±2

EXTENT OF SIGNAL ABNORMALITY (%LV)

	Reperfusion (n=7)	Non-reperfusion (n=3)
Occlusion	14±8*	19±11
Release	22±11**	20±11
Day 5	13±6	25±12*
Day 21	11±5	18±10
Pathology	10±6	17±9

*p<.05 **p<.01 vs control or pathology

Thus, 1) Reperfusion produces an abrupt marked rise in early T1 and T2 values to a greater degree than non-reperfusion. 2) The areas of early abnormal signal are not specific for infarction. 3) With reperfusion, on subsequent images, normalization of T2 occurs while T1 remains elevated, while without reperfusion, both T1 and T2 remain elevated.

EFFECTS OF HYDRALAZINE AND NITROGLYCERIN ON MYOCARDIAL pH, PERFUSION, AND FUNCTION DURING ACIDOSIS.

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To determine whether vasodilators would prevent the observed reduction in intracellular pH $[pH]_i$ and high energy phosphates (PCr,ATP) during acidosis, the effects of hydralazine (10^{-5} M) and nitroglycerin (2.5×10^{-5} M) on $[pH]_i$, PCr, and ATP were measured by N.M.R. spectroscopy. Coronary flow, developed pressure (DevP), and maximum dP/dT were also measured during 30 minutes of induced acidosis at high calcium concentration $[Ca]_o$, 4.0 mM, and during 15 minutes of re-equilibration in isolated perfused rat hearts (n=5).

$[Ca]_o$ (mM) Drug		4.0 -	4.0 hydralazine	4.0 nitroglycerin
		Results expressed as % of control (except pH_i)		
$[pH]_i$	acid.	6.42±.13	6.82±.09	6.80±.11
	re-eq.	died	7.10±.04	7.09±.03
PCr	acid.	35%±19	98%±11	69%±14
	re-eq.	died	103%±12	96%±16
ATP	acid.	68%±16	98%±10	76%±11
	re-eq.	died	103%±12	98%±16
Flow	acid.	51%±17	129%±19	98%±19
	re-eq.	died	122%±11	98%±19
DevP	acid.	29%±25	95%±9	73%±15
	re-eq.	died	110%±11	96%±3
dP/dT	acid.	12%±10	95%±13	70%±
	re-eq.	died	113%±7	100%±3

A decrease in coronary flow causes a decrease in PCr, ATP, DevP, and dP/dT, which is irreversible after 30 minutes of acidosis at high $[Ca]_o$. Preserving normal coronary flow with hydralazine or nitroglycerin prevents biochemical deterioration, allowing complete recovery.

SERIAL NUCLEAR MAGNETIC RESONANCE IMAGING IN ACUTE MYOCARDIAL INFARCTION IN MAN.

Lee R. Dilworth, M.D., Alex M. Aisen, M.D., G.B. John Mancini, M.D., F.A.C.C., Kenneth A. Buckwalter, M.D., Andrew J. Buda, M.D., F.A.C.C. University of Michigan, Ann Arbor, Michigan.

Gated nuclear magnetic resonance (NMR) imaging has been shown to distinguish infarcted from normal myocardium during initial hospitalization for acute myocardial infarction (MI). To determine whether the NMR appearance of infarcted myocardium changes during the early post-MI period, we studied 5 patients (with EKG- and enzyme-documented MI) at 3-5 days post-MI (acute) and again at 10-14 days post-MI (pre-discharge). Using a 0.35 Tesla NMR system with a spin-echo (SE) pulse sequence, first and second SE NMR images were obtained using transverse acquisition, as well as coronal acquisition with the patient in the 30° RAO position. Intensities of infarcted and normal-appearing myocardium were measured from regions of interest (100 voxels) defined on the acute image best demonstrating the MI, and from the corresponding pre-discharge image. With both spin-echo techniques, infarct intensity was greater than normal intensity in both acute and pre-discharge ($p < .05$) studies. Similar results were obtained in comparing T2 relaxation times. Results of % difference of regional intensity (intensity of infarcted region - intensity of normal region/intensity of normal region) are summarized below (mean±SEM):

FIRST SE		SECOND SE	
Acute	Pre-discharge	Acute	Pre-discharge
33.3±19.8	40.3±11.6*	41.3±18.1	40.1±8.6*

* p=NS, pre-discharge vs. acute

We conclude that NMR imaging can differentiate normal from infarcted myocardium during the early post-MI period. However, no significant change occurred in the relative intensity of infarcted and normal myocardium between 4 and 12 days post-MI.

CALCULATION OF LEFT VENTRICULAR VOLUMES AND EJECTION FRACTION FROM MAGNETIC RESONANCE TOMOGRAMS USING A COMPUTERIZED 3-D RECONSTRUCTION: COMPARISON WITH VENTRICULOGRAPHY Randall Thompson, MD, Robert Edelman, MD, Howard Kantor, MD, PhD, Marcia Leavitt, Douglas Miller, MD, Robert Okada, MD, FACC, Thomas Brady, MD, and Robert Dinsmore, MD. Massachusetts General Hospital, Boston, MA.

Magnetic resonance provides high resolution tomographic images which have the potential for measurement of LV volumes without problems of geometric assumptions inherent to other methods. To determine the accuracy of a new method of measuring LV volume and ejection fraction (EF) by magnetic resonance (MR) imaging we studied 7 patients who had undergone biplane left ventriculography (LVG) 24 hours prior. Spin echo MR images were obtained through the LV short axis. MR volume measurement was facilitated by the use of a technique of short echo delays (TE=15 or 20 msec) which we have recently reported. This made it possible to obtain 5-8 contiguous tomograhic images from aortic valve to LV apex within the same phase of the cardiac cycle. With the use of a computerized semi-automated edge detection system, 3-D reconstructions of the LV endocardial shell were obtained from systolic and diastolic MR images. Volumes and ejection fraction were calculated and compared with LVG measurements.

Results: There was a close correlation between measurements from MR 3-D LV reconstruction and LVG calculated values for systolic volume ($r=.91$, $p<.005$), diastolic volume ($r=.82$, $p<.01$), and ejection fraction ($r=.88$, $p<.01$).

Conclusion: Contiguous short axis MR tomograms in the same phase of the cardiac cycle are virtually free of geometric assumptions and combined with computerized 3-D analysis provide accurate assessment of LV volumes and EF.

CHARACTERIZATION OF MYOCARDIAL SIGNAL INTENSITY BY MAGNETIC RESONANCE IMAGING IN PROVEN NORMAL AND INFARCTED MYOCARDIAL SEGMENTS.

Robert E. Dinsmore M.D., F.A.C.C., Jennifer A. Johns M.B.B.S., F.R.A.C.P., Tsunehiro Yasuda M.D., Gary L. Wismer M.D., Donald L. Johnston M.D., Thomas J. Brady M.D., Robert C. Leinbach M.D., F.A.C.C., Randall Thompson M.D., Herman K. Gold M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA.

Magnetic resonance imaging (MRI) has shown increase in left ventricular (LV) myocardial signal after myocardial infarction (MI), however signal intensity (SI) varies widely between subjects. To define easily obtained standardized criteria for identification of normal (NMS) or infarcted myocardial segments (IMS), we studied 19 pts who underwent thrombolytic therapy with either tissue plasminogen activator or streptokinase within 6 hours of onset of MI. Coronary reperfusion was achieved in 12. Spin echo 30 and 60 msec cardiac MRI at 0.6 Tesla was performed 5-13 (mean 9) days and repeat coronary arteriography and biplane left ventriculography (LVA), 10 days post-MI. Multiple systolic images oriented to the true LV short axis from aortic valve to apex were obtained, allowing precise correlation of LV segments on MRI with LV segments on LVA. SI was then measured in proven NMS and IMS and in adjacent skeletal muscle (SM). There was no significant difference in SI between reperfused and non-reperfused IMS. The difference between NMS and IMS in SI units corrected for SM was highly significant (1.5 ± 0.4 vs 2.5 ± 0.6, $p < 0.0001$).

Thus, these data provide easily obtained standardized criteria for definition of normal and infarcted MS in recent MI in humans.

EFFECT OF MANNITOL ON MAGNETIC RESONANCE RELAXATION PARAMETERS IN CANINE MYOCARDIAL INFARCTION: RELATIONSHIP TO TISSUE WATER AND MYOCARDIAL BLOOD FLOW

D. Douglas Miller, M.D., Howard L. Kantor, M.D., Donald L. Johnston, M.D., Shunichi Homma, M.D., Randall Thompson, M.D., Thomas J. Brady, M.D., Robert D. Okada, M.D., F.A.C.C.,Massachusetts General Hospital, Boston,MA.

To assess the effect of hyperosmotic mannitol on regional T1 and T2 after myocardial infarction (MI), 7 dogs had a 3 hr left anterior descending coronary artery occlusion followed by 1 hr of reperfusion. Mannitol (12.5gm/50ml) was infused intravenously at 15.3 ml/min for 15 min before and after release to obtain a 40 mosmo rise in serum osmolarity. Microsphere myocardial blood flow (MBF) was measured at peak occlusion(o) and 15 min. of reperfusion(r). Excised hearts were wrapped in parafilm, imaged in a small bore (1.4 T) superconducting magnet, then T.T.C. stained. Spectrometer (20MHz) T1 and T2, % water content($\%H_2O$), and MBF were calculated in 100 T.T.C.(-)/MI and normal endocardial segments for comparison to 9 untreated control dogs. T1 and T2 were lower in normal (T1: 593±14vs659±8ms; T2: 43±5vs49±1ms) and MI segments (T1: 623±26vs751±18ms; T2: 48±6vs55±1ms) of mannitol dogs ($p<0.05$). T1 and T2 did not correlate with $\%H_2O$, MBFr or MBFo(0.67±.1 ml/min/gm) in normal segments of mannitol dogs. In MI segments of mannitol dogs, MBFo(0.06±.1 ml/min/gm) was lower and T1, T2 were 5% and 12% greater than normal ($p<0.001$). T1 and T2 of MI segments correlated with MBFo ($p<0.001$), and rose exponentially as MBFo approached zero in untreated (T1:r=.87;T2:r=.81) and mannitol dogs (T1:r=.54;T2r=.50). The difference in $\%H_2O$ between MI and normal segments was smaller in mannitol dogs (79vs77±3%; $p<0.01$). In MI segments, T1 correlated better than T2 with $\%H_2O$ (r=.41vs .30; $p<0.05$). When the effect of $\%H_2O$ was controlled for, T1 and T2 correlated less well with MBFo. T1-dependent inversion recovery and T2 spin-echo images had reduced contrast between the MI and normal zones of mannitol dogs compared to controls.
We conclude that mannitol, an agent that reduces myocyte edema, decreases the $\%H_2O$ and MR relaxation parameters of infarcted>normal myocardium. Occlusion myocardial blood flow and $\%H_2O$ are interdependent determinants of MR relaxation times (T1>T2) in infarcted segments. Mannitol-induced redistribution of myocardial water reduces in vitro (T1) and MR image (T1 and T2) contrast between infarcted and normal myocardium.

CORONARY ARTERY GRAFT PATENCY AS ASSESSED BY MAGNETIC RESONANCE IMAGING

Hugh G Love, MB BS, MRCP, MRCS; Jeremy PR Jenkins, MBChB, MRCP(UK), DMRD, FRCR; Christopher J Foster, MBChB, MRCP(UK); Derek J Rowlands, MD, FRCP and Ian Isherwood, MBChB, DMRD, MRCP, FRCR
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The aim of this study was to assess patency of coronary artery bypass grafts by Magnetic Resonance (MR) imaging compared with Computed Transmission Tomography (CT) or coronary graft arteriography.

18 patients were studied pre- and post-operatively on a Picker International superconducting magnet operating at 0.26 Tesla. Images were obtained in three orthogonal planes at end-diastole and end-systole. Graft patency was also assessed either angiographically or by CT. A total of 49 grafts were studied. 31 grafts were considered patent by MR imaging, 34 by CT and/or angiography. 18 grafts were not visualised by MR imaging, 3 of which were detected as patent by the other method. These grafts were either proximally stenosed or had a poor blood flow velocity pattern. The sensitivity of MR imaging is 0.93 for the detection of graft patency.

It is concluded that MR imaging can detect a normally functioning coronary artery bypass graft. It is envisaged that MR imaging may provide a non-invasive screening technique for assessment of coronary artery bypass graft patency in patients presenting with post-operative angina.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 9:00AM–10:00AM
Hall D, Georgia World Congress Center
Nuclear Cardiology/Single Photon Radionuclides

INDIUM-111 LABELED MONOCLONAL ANTIFIBRIN SPECIFIC ANTIBODY FOR DETECTION OF CLOT

Michito Kanke, M.D., Ban An Khaw, Ph.D., Chiau S. Liau, M.D., Tsunehiro Yasuda, M.D., Gary Matsueda, Ph.D., Edgar Haber, M.D., F.A.C.C., Kenneth A. McKusick, M.D., H. William Strauss, M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA

The monoclonal antifibrin antibody (64C5) binds specifically to human fibrin, and crossreacts with canine fibrin. Clot imaging with In-111 labeled antifibrin antibody was performed in 6 dogs. In all dogs, thrombi were formed in the isolated left jugular vein by mixing thrombin and barium with blood. Thrombi were released 30 minutes later. In addition, copper coils were injected from the left jugular vein in 3 of 6 dogs. Four hundred-500 μCi of In-111 64C5 and 80-100 μCi of I-125 nonspecific Ig G were injected intravenously one hour after release of thrombi. Clot imaging were performed in the anterior, LAO, RAO, left lateral, right lateral, posterior, LPO and RPO views 20-24 hours following intravenous administration. The dogs were killed and the lungs and hearts were excised, followed by gamma imaging and X-ray confirmation of the thrombi. Then the uptake of radioactive tracers in tissue samples were determined by scintillation counting.
The weight of the smallest clot that was visible in in vivo planar images was 50.6 mg. The clot images of the excised lungs corresponded to the copper coil or barium clot of x-ray photograph. The (%dose/gm) tissue localization are as follows:

Sample	In-111 64C5		I-125 Nonspecific Ig G	
	Mean	SE	Mean	SE
PA clot (copper coil)	0.181	0.025	0.019	0.004
PA clot (barium)	0.243	0.068	0.012	0.002
RA clot (copper coil)	0.102		0.021	
infarcted lung	0.015	0.004	0.023	0.007
normal lung	0.010	0.005	0.019	0.009
liver	0.051	0.008	0.019	0.016
kidney	0.018	0.004	0.021	0.008
spleen	0.022	0.002	0.018	0.017
skeletal muscle	0.001	0.001	0.002	0.001
heart muscle	0.005	0.001	0.008	0.002
blood	0.029	0.004	0.034	0.030

These results suggested that monoclonal antifibrin antibody (64C5) could specifically detect RA and PA clot.

MYOCARDIAL WASHOUT RATE OF THALLIUM-201: COMPARISON BETWEEN REST, DIPYRIDAMOLE WITH AND WITHOUT AMINOPHYLLINE, AND EXERCISE STATES. George T O'Byrne, MB; Jamshid Maddahi, MD, FACC; Kenneth F Van Train, BS; John D Friedman, MD; Daniel S Berman, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, CA

Evaluation of regional percent washout of thallium-201 (Tl-201) may be a useful adjunct in the detection of hypoperfused myocardial regions; however, the relationship between washout rate and type of Tl-201 procedure being performed has not been previously examined. Thus, we undertook the present study to compare the percent washout of myocardial Tl-201 in various states in 88 patients with a <1% likelihood of CAD. Tl-201 was injected intravenously at rest in 17, following dipyridamole (dipy) (0.56 mg/kg) with hand-grip exercise but without aminophylline (A-) in 10 and with aminophylline (A+) in 12, and following exercise in 49 patients. Ten-minute images were obtained early (5-10 minutes) and 4 hours after Tl-201 injection. Following interpolative background subtraction and 9-point smoothing, initial distribution and % washout circumferential profiles were generated. The mean ± standard deviation for regional washout rate of Tl-201 for each procedure was as follows:

	Rest	Dipy A-	Dipy A+	Stress
Mean % W/O	-1.7	34.2	42.5	53.7
SD	25.5	12.2	14.9	9.6

The % washout was progressively higher between rest, dipy A-, dipy A+, and stress states. The variability of % washout was progressively lower in rest, dipy, and stress states. We conclude that the normal % washout of myocardial Tl-201 depends on the type of Tl-201 test being performed. For clinical purposes, specific sets of normal limits for each type of test are needed for accurate detection of washout abnormality.

CAN RESTENOSIS AFTER CORONARY ANGIOPLASTY (PTCA) BE PREDICTED BY EXERCISE FIRST PASS RADIONUCLIDE ANGIOCARDIOGRAPHY? George Pilcher, M.D., E. Gordon DePuey, M.D. FACC, Mark A. Libow, M.D., Gary S. Roubin, MB, Ph.D., John S. Douglas, M.D. FACC, Spencer B. King, M.D. FACC, Harvey J. Berger, M.D. FACC, Emory University School of Medicine, Atlanta, GA.

To determine if exercise (ex) first pass radionuclide angiocardiography (RNA) can predict vessel status after PTCA, RNA was performed within 3 days after PTCA and compared prospectively to coronary angiography obtained 5.9 ± 2.6 months (mean ± SD) after PTCA in 104 patients (pts). Successful single vessel (SV) PTCA (>20% reduction in diameter stenosis) was performed in 99 pts with SV disease and 5 pts with double vessel disease. Mean luminal diameter stenosis (DS) was reduced from 71 ± 13% to 20 ± 10% ($p<0.001$). At angiographic restudy, 39 pts had restenosis (>50% DS), averaging 71 ± 15% compared with 26 ± 12% ($p<0.001$) in the remaining 65 pts. Abnormal ex left ventricular (LV) reserve by RNA was defined as a fall in LV ejection fraction with ex. All 104 pts were asymptomatic at time of ex RNA. Abnormal ex RNA occurred in 32/104 pts, 24 with restenosis and 8 with continued patency. The value of an abnormal ex RNA in predicting restenosis was 75% (24/32 pts). The value of a normal ex RNA in predicting continued vessel patency at restudy was 79% (57/72 pts). The sensitivity and specificity of ex RNA post-PTCA were 62% and 88% respectively. Evaluation of regional wall motion did not improve the utility of ex RNA.

Thus ex RNA obtained prior to discharge post-PTCA appears helpful in predicting restenosis. The time of recurrence is variable, but these data suggest that it may occur as early as the immediate post-PTCA period.

LEFT VENTRICULAR FUNCTION IN NORMAL SUBJECTS: SEX AND AGE RELATED EFFECTS AT REST AND DURING EXERCISE. Robert O. Bonow, MD, FACC, Stephen L. Bacharach, PhD, Michael V. Green, MS, Felipe C. Robinson, MD, Edward Lakatos, PhD, Richard O. Cannon, MD, FACC, Neal R. Cutler, MD, and Steven M. Larson, MD, NHLBI, Bethesda, Md.

Previous studies of upright exercise demonstrate a sex-related difference in the LV ejection fraction (EF) response to exercise; EF increases with exercise in men, but is unchanged and may even decrease in women. To assess the effect of supine exercise on LV function, we performed radionuclide angiography in 66 normal subjects age 21-77: 42 men (age 43±15) and 24 women (age 41±17). The increase in EF with maximal exercise (max ΔEF) declined linearly as a function of age ($r=.50$, $p<.001$), and was less in subjects older than compared to younger than 45 yrs (7±4 vs 16±6%, $p<.01$). Max ΔEF also differed between men (13±6%) and women (10±6%), which was significant when adjusted for age ($p<.01$). Both men and women decreased end-systolic volume similarly at max exercise, but men increased end-diastolic volume (14% vs 0%, $p<.005$) and hence stroke volume (39% vs 14%, $p<.001$) to a greater extent than women. However, men achieved greater max workloads with greater cardiac output augmentation (ΔCO) and greater blood pressure (BP). When compared at workloads of equivalent ΔCO and BP, men and women did not differ in either LV volumes or ΔEF. Although EF at rest was unrelated to age, resting peak filling rate (PFR) decreased ($r=.54$, $p<.001$) and time to PFR increased ($r=.58$, $p<.001$) with age in both sexes. Thus, aging does not affect LV systolic function at rest but significantly influences LV diastolic function at rest and the LV EF response to exercise. The greater max ΔEF achieved by men may reflect the greater workloads attained, differences in peripheral vascular responses to exercise, or intrinsic differences in LV function compared to women.

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RESPIRATORY VARIATIONS IN RIGHT VENTRICULAR FUNCTION.
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Respiratory effort during inspiration (I), expiration (E) and Valsalva (V) results in changes in RV preload and afterload. To investigate the effects of these on RV ejection fraction (EF), first-pass radionuclide angiography with gold-195m (half-life 30.5 sec) was perfomed in 17 subjects at maximal I and E, and in 8 subjects at rest and during V. RVEF on I was 32±11% (mean±SD) and fell to 26±10% on E ($p<0.01$). This represents a fall of 18% of the I value. 15 subjects showed a fall on E and only 2 a rise. There were no significant changes in bolus duration, RV transit time, or the number of RV cycles, all of which might have been expected to rise during E. V caused a rise in RVEF from 29±7% to 43±10% ($p<0.001$), and all subjects showed a rise. V also prolonged bolus duration from 0.9±0.3 sec to 2.7±1.8 sec ($p<0.05$), increased transit time from 3.3±0.9 sec to 5.3±2.3 sec ($p<0.05$), and increased the number of cycles from 4.1±1 to 7.8±4 ($p<0.05$). Qualitative analysis of time activity curves from the superior vena cava suggested the development of tricuspid regurgitation. In conclusion RVEF is higher on I than on E in most subjects. V causes a rise in in RVEF with development of tricuspid regurgitation and prolongation of RV transit. These data suggest 1) the relative influences of venous return, pulmonary artery pressure and possible functional tricuspid regurgitation vary during I, E and V and affect RVEF and 2) caution in the interpretation of changes in RV function on exercise when imaging occurs during maximal respiratory effort.

A SENSITIVE MEANS TO DIAGNOSE MYOCARDIAL INFARCTION IN MAN: I-123 PHENYLPENTADECANOIC ACID MYOCARDIAL IMAGING.
Patrick L. Kennedy, M.D., Christopher L. Wolfe, M.D., Padamakar V. Kulkarni, Ph.D., Donald E. Jansen, M.D., Christopher L. Hansen, M.D., Gregory I. Gabliani, M.D., Robert W. Parkey, M.D., F.A.C.C., L. Maximilian Buja, M.D., F.A.C.C., and James R. Corbett, M.D., Univ of Texas Health Sci Ctr, Dallas, TX.

I-123 phenylpentadecanoic acid (IPPA) has shown promise as an imaging agent in animal models. The goal of this study was to assess the utility of IPPA myocardial scintigraphy in diagnosing myocardial infarction (MI) in patients (pts). Nineteen pts with prior documented MI were evaluated. In these pts, there were 13 Q-wave (7 anterolateral, 6 inferior) and 6 non-Q-wave infarcts. Two-6 millicuries of IPPA were injected intravenously at rest or at peak symptom-limited exercise. Planar imaging was performed beginning at 4 minutes post-injection and continued for 60 minutes. Quantitative segmental analysis was performed and results were compared to that of 20 normal volunteers (NLS). NLS demonstrated relatively homogeneous initial IPPA activity, varying by 18±7% at rest and 13±5% following exercise. In pts studied at rest with IPPA, 14/15 infarct-related segments demonstrated decreased initial IPPA activity (39±15%, $p<0.001$), and 8/15 demonstrated delayed early IPPA washout (6.3±3.8%, $p<0.001$). In pts studied following exercise, 11/11 infarct-related segments demonstrated decreased initial IPPA activity (35±15%, $p<0.001$). Two of 11 demonstrated slow, 7/11 normal, and 2/11 enhanced IPPA segmental washout. No correlation was apparent between the presence of a Q-wave infarct and the rate of IPPA washout. We conclude that: (1) high-quality myocardial images can be obtained at rest and following exercise with IPPA; (2) NLS demonstrate relatively uniform uptake and washout of IPPA; (3) infarcted myocardial segments are characterized by decreased initial IPPA activity and heterogeneity of IPPA washout at rest and following exercise.

QUANTITATION OF EXTENT, DEPTH AND SEVERITY OF DEFECTS IN PATIENTS UNDERGOING EXERCISE PLANAR THALLIUM-201 SCINTIGRAPHY.
Steven Reisman, MD; Jamshid Maddahi, MD, FACC; Kenneth Van Train, BS; Daniel Berman, MD, FACC. VA Med Ctr, Long Beach, & Cedars-Sinai Med Ctr, Los Angeles, CA

We studied 133 patients (pts) undergoing exercise planar Tl-201 (Tl) scintigraphy and coronary arteriography to develop a method for quantitative (Q) analysis of extent (E) of myocardium with reduced Tl uptake, depth (D) of reduction of Tl uptake, and Tl defect severity (Sev) which combines E and D by integrating the total area below mean normal. Circumferential profiles for 3 exercise views were compared to mean profiles from 49 normals to obtain 3 Q scores (S): QES, QDS, QSevS. Visual (V) Tl analysis used a 4-point S system for 15 segments (segs) in 3 views: VES=# abnormal segs, VDS=highest 4-point S (0-3) per pt in any seg, and VSevS=summed S in 15 segs. Q and V S of E, D and Sev were compared. A close correlation was found between QES and VES (r=.73) and QSevS and VSevS (r=.79). For identification of pts with the high-risk pattern of a severe stress Tl defect (VDS=3), QDS of ≥36 had 81% sensitivity and 82% specificity. With increasing extent of CAD a significant ($p<.05$) increase in QSevS and QES was noted:

	0 Vessel	1 Vessel	Multivessel
QSevS	382±226	906±790	1086±814
QES	42±16	58±22	64±20

Pts with exertional hypotension also had higher QSevS (1558±920 vs 834±715, $p<.05$) and QES (74±20 vs 57±21, $p<.05$) than those without exertional hypotension. Thus, computerized quantitation of extent, depth and severity of planar Tl defects: 1) is representative of expert visual analysis, 2) corresponds with exercise-induced hemodynamic abnormalities, 3) may help identify patients with extensive CAD and jeopardized myocardium, and 4) may prove useful in objectively detecting pts with high-risk scintigraphic and/or coronary arteriographic patterns.

LINEAR CORRELATION BETWEEN XENON-133 AND MICROSPHERE MEASUREMENTS OF MYOCARDIAL BLOOD FLOW OVER A WIDE RANGE OF FLOWS.
Steven C. Port, M.D., F.A.C.C., Carl W. Christensen, Ph.D., Raymond P. Grenier, M.S. and Donald H. Schmidt, M.D. University of Wisconsin, Mount Sinai Medical Center, Milwaukee, WI.

It has been suggested that the xenon-133(Xe) washout method is inadequate for measurement of the elevated myocardial blood flow(MBF) seen with vasodilators such as dipyridamole and adenosine. In this study Xe and microsphere(MS) measurements of MBF at baseline and after intracoronary adenosine were compared in 17 open-chest dogs with a cannulated coronary artery. Xe was injected into the cannulated vessel and MS were injected into the left atrium. In addition, a right atrial Xe injection was performed and washout of Xe in the lung was recorded in the same hemodynamic state as the immediately preceding myocardial measurement. The myocardial Xe curves were corrected by a frame by frame, pixel by pixel subtraction of the normalized lung curve within the myocardial territory. Monoexponential analysis of the corrected curve from peak to 50% peak activity gave a linear correlation of 0.97 ($y=0.81x+13.9$, SEE 30.7) with the MS results over a range of flows from 41-536 ml/100gm/min. When the vascular space factor of the Kety-Schmidt equation (vascular volume/myocardial volume) is assumed to be 0.05 at control and 0.10 during adenosine, then there is no significant difference ($y=0.94x+6.8$, $r=0.96$, p=NS) between xenon and microsphere flows.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 11:00AM–12:00NOON
Hall D, Georgia World Congress Center
Pharmacology—Clinical

ANTIANGINAL EFFECT OF CV-4151, A NEW, POTENT, SELECTIVE INHIBITOR OF THROMBOXANE SYNTHETASE.

Yoshihiro Kimura, M.D., Kazuhisa Kodama, M.D., Masashi Naka, M.D., Shinsuke Nanto, M.D., Koichi Taniura, M.D., Tsunehiko Kuzuya, M.D., Yasuhiko Hamanaka, M.D., Michihiko Tada, M.D., F.A.C.C., Cardiovascular Division of Osaka Police Hospital, Osaka, Japan.

We studied the effect of CV-4151 ((E)-7-phenyl-7-(3-pyridil)-6-heptenoic acid), a new thromboxane synthetase inhibitor, on the platelet activity and anginal attack of 22 patients with unstable angina. Frequency of angina (AP), collagen(0.5μg/ml)-induced aggregation of platelet rich plasma, and immunoreactive thromboxane (TX) B_2 of plasma were measured before and during administration of CV-4151 (50mgx2/day). During administration platelet aggregability markedly decreased in 11 cases (responder), but remained unchanged in 11 cases (non-responder), whose platelet aggregability before dosing was lower than that of former cases. During dosing, plasma TXB_2 levels significantly decreased (318±60 to 242±62pg/ml plasma, mean±SEM, $p<.05$, n=16). Antianginal effect of CV-4151 (AP/week) is shown below (mean±SEM, *$p<.05$ vs before);

	before	1st week	2nd week	4th week
Responder	8.6±1.3	6.2±1.5	4.7±1.6	3.4±3.4*
Non-responder	6.5±1.8	3.6±1.2	2.7±0.9	2.5±0.8*

Discontinuation of CV-4151 resulted in increasing in AP in almost all patients. No significant side effect was observed during administration. These data suggest that CV-4151 has beneficial effects on unstable angina, probably due to reduction of platelet aggregability and TXA_2 production. Whether the augmentation of local prostacyclin production may contribute to this antianginal effect should further be sought.

PREVENTION OF CORONARY ARTERIAL SPASM WITH A THROMBOXANE SYNTHETASE INHIBITOR

François A. Thieuleux, M.D., Jean M. Lablanche, M.D., François A. Lombard, M.D., Pierre E. Nocon, M.D., Michel E. Bertrand, M.D., F.A.C.C. University of Lille. France

Dazoxiben (D), an inhibitor of thromboxane synthetase could be useful in the treatment of patients with coronary arterial spasm (CAS). The following protocol was designed in 10 patients (pts) (mean age : 51 yrs) with documented CAS. The study consisted of 4 phases of 2 days. Phase 1 and 3 were a placebo period (P1 and P2). During phase 2 and 4, the patients were randomly assigned to D (400 mg/day) or nifedipine (N) (60 mg/day). During each phase, a 24 hour ambulatory monitoring was recorded and a provocative test with incremental doses of ergometrine (E) was performed. The criterion for a positive test was an ST segment change > 1 mm.

	Phase 1	D	Phase 3	N
Number of attacks	15.5±7	6.4±2	11.6±5	3.2±1.3
Positive E test	10+	10+	10+	7+
Ergo. threshold (mg)	0.33±0.07	0.26±0.5	0.24±0.03	0.44±0.07*

m ± SEM * $p < 0.05$

In conclusion, the inhibitor of thromboxane synthetase (D) failed to prevent coronary arterial spasm

A DOUBLE-BLIND TRIAL OF DILTIAZEM IN THE TREATMENT OF RAYNAUD'S PHENOMENON

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Eleven patients with Raynaud's phenomena were entered into a randomized double-blind crossover study of diltiazem versus placebo. The study group was composed of five men and six women. Four were found to have primary Raynaud's disease and seven were found to have Raynaud's phenomenon secondary to connective tissue disease. Digital skin temperature recovery time (STRT) was measured after immersing the patients hand in ice water. Baseline measurements were obtained and then patients were randomized to receive either diltiazem 30mg QID or placebo for two weeks followed by a crossover phase. The mean STRT during the control phase was 62 +/- 31 min., after two weeks of diltiazem therapy STRT was 41 +/- 39 min. ($p=.056$). After two weeks of placebo therapy the mean STRT was 50 +/- 33 min ($p=.183$). Subjectively, 8 of the 11 patients felt they were improved on Diltiazem, two of these reported marked improvement, experiencing no attacks during the two week treatment period. Diltiazem was universally well tolerated, with one patient developing transient diarrhea. We have shown a subjective improvement in symptomatic patients with a trend toward a significant objective benefit. We feel that diltiazem, in view of its lack of side-effects, is an effective alternative therapy for the treatment of symptomatic Raynaud's phenomenon.

POTENTIAL ADVERSE EFFECTS OF PENTOXIFYLLINE ON LIMB HEMODYNAMICS IN PATIENTS WITH INTERMITTENT CLAUDICATION.

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Pentoxifylline (Pfx) reportedly improves walking capacity in patients (pts) with intermittent claudication (IC). A hemorheologic mechanism is supported by greater erythrocyte flexibility *in vitro* and oxygen tension in skeletal muscle at rest. We studied the limb hemodynamic (Hd) response to hyperemia following exercise (Ex) and release of arterial occlusion (AO) by venous occlusion plethysmography in 8 pts (65±6 year) with chronic (5.5±2.4 year) IC (156±52 meters). Measurements were made before and after two months oral therapy with Pfx, 400 mg t.i.d. and two hours after 800 mg acute dosing. Table shows changes (Δ;%) in blood flow (BF; ml/100ml tissue/min), pressure (BP; mmHg) and resistance (VR; units) as mean±SEM: (Student t-test).

	Placebo	Pfx	P
Rest BF	6.1 ± 0.9	5.2 ± 0.5	NS
Rest BP	93 ± 4	92 ± 5	NS
Rest VR	18.1 ± 3.6	22.9 ± 3.9	NS
Ex BF	16.4 ± 2.5	13.1 ± 2.4	<0.10
Ex VR	8.3 ± 1.4	10.1 ± 1.6	<0.025
AO BF	17.2 ± 2.7	14.1 ± 1.6	<0.10
AO VR	9.9 ± 1.9	12.9 ± 3.0	<0.05
AO Δ%VR	-37 ± 13	-22 ± 16	NS

Long term treatment produced no significant changes in IC (141±50 meters; NS) and clinical deterioration occurred in 3 pts. The rise in hyperemic VR implies an adverse effect on blood flow properties in the ischemic limb. These findings do not support a beneficial effect upon exercise tolerance, hemodynamics or hyperemic perfusion during maintenance therapy with pentoxifylline and suggest a detrimental effect in some patients.

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ATROPINE UNMASKS BEDREST DECONDITIONING EFFECT IN HEALTHY MEN: SPECTRAL ANALYSIS OF INTERBEAT INTERVALS

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Bedrest deconditioning is suspected to reduce cardiac function. However, quantitation of subtle decreases in cardiac reserve may be difficult. Normal subjects show considerable variability in heart rate response, reflected by a relatively broadband interbeat interval power spectrum. We hypothesized that the deconditioning effects of bedrest would induce narrowing of this spectrum, reflecting a reduction in the autonomically-modulated variability in heart rate. Ten aerobically conditioned men (35-50 years) underwent orthostatic tolerance testing with lower body negative pressure pre-bedrest and after 10 days of bedrest, while on placebo and after intravenous atropine. Spectra were derived by Fourier analysis of 128 interbeat interval data sets from subjects with sufficient numbers of beats during matched periods of the protocol. Root-mean-square (RMS) values ($\bar{X}\pm SD$) for the band encompassing the 2nd to 64th harmonics were computed.

Condition	Placebo RMS (n=6)		Atropine RMS (n=7)
Pre-bedrest	P=NS	93±33 ms	P<.01 63±24 ms
Bedrest		84±38 ms	40±23 ms

These data suggest that atropine unmasks the deconditioning effect of bedrest in athletic men, evidenced by a reduction in interbeat interval spectral power not apparent with placebo. Spectral analysis offers a new means of quantitating the effects of bedrest deconditioning and autonomic perturbations on cardiac dynamics.

ESMOLOL FOR HYPERTENSION EARLY AFTER CARDIAC SURGERY.

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Systolic hypertension (HTN) early after cardiac surgery (CS) is common, threatens fresh anastomoses, and increases cardiac work. Because it is predominantly associated with elevated catecholamines and preop beta-blocker use; we evaluated the efficacy of Esmolol (Es), an ultrashort-acting beta-blocking agent. Twelve pts (18-28 hrs post CS; CABG 9, AVR 3) received controlled infusions of Es (142±100 ug/kg/min; 50 to 300) and nitroprusside (NTP) (1.6±1.3 ug/kg/min; 0.5 to 2.75) by randomized sequence. No complications occurred. Therapeutic response (≥15% SBP reduction) was rapidly achieved in 11/12 Es (mean 22±16 mins) and 12/12 NTP pts (mean 10±10 mins). Hemodynamic effects were as follows: (*p<.05 Es vs NTP).

	Control	Es	Control	NTP
HR*	94±14	82±11	97±14	104±15
SBP	170±12	136±14	173±11	141±15
DBP	69±14	63±14	72±15	50±15
PCW	13±4	15±3	14±4	10±3
CI*	2.9±.4	2.2±.3	3.0±.5	3.2±.5
SVI	31±4	28±4	31±4	31±2
SVR	1506±362	1593±432	1491±391	1060±267
LVSWI	57±8	40±6	59±10	48±7
O_2 SAT*	98±2	98±1	98±1	94±3

Thus, for HTN early after CS, Es is safe, effective and rapid. Compared to NTP less unwanted decrease in DBP and O_2 SAT is seen, but there is more decrease in HR and cardiac index.

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SHOULD NITRATES OR NIFEDIPINE BE PREFERRED AS FIRST-LINE ANTI-ANGINAL THERAPY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION?

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Both nifedipine (NIF) and isosorbide dinitrate (ISDN) relieve angina and ameliorate loading conditions in the normal heart, but their effects have not been compared in the same patients (pts) with left ventricular dysfunction (LVD). To do so, 16 pts with LVD (LV ejection fraction < 30%) received NIF (20 mg orally) and ISDN (40 mg orally) in random order on alternate days. Cardiac index (CI, l/min/m^2), stroke volume index (SVI, ml/beat/m^2), heart rate (HR, bpm), mean arterial (MAP), LV filling (LVFP) & mean right atrial pressures (RAP, mm Hg), systemic vascular resistance (SVR, d-s-c) and LV stroke work index (LVSWI, g-m/m^2) were measured before (C) and at peak effect of each drug, where * = p<.05 (C vs drug); † = p<.05 (NIF vs ISDN):

	CI	SVI	HR	MAP	LVFP	RAP	SVR	LVSWI
C	1.7	22	83	86	28	15	2033	17
NIF	2.1*	25*	82	62*	26	17	1015*	14
C	1.8	24	83	83	27	15	1857	18
ISDN	2.1*	28*	80*	72*†	17*†	9*†	1495*†	20*†

Although NIF produced more marked ↓ in SVR than did ISDN (-50% vs -19%), this was translated into a greater ↓ in MAP and not a greater ↑ in CI or SVI (which ↑ similarly with both drugs). ISDN produced dramatic ↓ in LVFP and RAP, whereas NIF did not, because NIF lacked ISDN's venodilator actions. Hence, LV performance (LVSWI vs LVFP) was shifted favorably with ISDN but failed to improve with NIF, despite its more marked effects on SVR. This likely resulted from NIF's negative inotropic actions, which limited the ↑ in CI that could occur in response to a ↓ in SVR. Such cardiodepression was dramatic in 4 pts, who deteriorated clinically after NIF; none did so after ISDN.

In conclusion, in pts with left ventricular dysfunction, ISDN improves LV performance to a greater degree and is better tolerated hemodynamically and clinically than NIF.

MOLSIDOMINE, A NITRATE-LIKE SUBSTANCE WITH MARKED ANTI-ISCHEMIC AND ANTIANGINAL EFFICACY AND NO TOLERANCE DEVELOPMENT DURING LONG-TERM TREATMENT

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Molsidomine is a substance with nitrate-like properties, for which it has not been established whether tolerance develops similar to that associated with nitrates. Accordingly to address this question as well as to assess the extent and duration of action this study with molsidomine s.r. 8 mg t.i.d. in 10 patients with documented coronary artery disease and stable reproducible angina pectoris was carried out. A placebo-controlled, double-blind, crossover protocol was employed with testing acutely and after 4-week treatment periods with exercise studies performed before and at 1 and 5 hours after medication on the 1st and 28th day. As compared with placebo, the reduction in ST-segment depression (ST) as well as exercise capacity to onset of 1 mm ST-segment depression (ST-1), rate of anginal attacks and daily nitrate consumption was analyzed.

	day 1		day 28	
	1 h.	5 h.	1 h.	5 h.
ST	-88%*	-51%*	-81%*	-34%*
ST-1	+79%*	+35%*	+80%*	+23%*

* = sign.

There was a decrease in the rate of anginal attacks of 90% and nitrate consumption of 83%. Thus a dosage of 8 mg t.i.d. molsidomine s.r. elicited a marked and long lasting antiischemic and antianginal effect, which was documented to be of comparable extent both after acute administration as well as during long-term treatment.

EFFECTS OF LOW DOSE NICARDIPINE ON SYSTEMIC AND CORONARY HEMODYNAMICS DURING RAPID ATRIAL PACING IN PATIENTS WITH ISCHEMIC HEART DISEASE.

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NICARDIPINE (NIC), a calcium antagonist, has been reported to feature greater coronary than systemic vasodilator capacity without associated negative inotropism. To determine if NIC without systemic effects benefit ischemic patients (pts) during stress, we measured in 10 pts with left coronary stenosis, aortic pressure (AoP mmHg), cardiac index (CI l/min/m^2), maximal dp/dt (mmHg/sec), coronary sinus thermodilution flow (CSF ml/min), myocardial lactate extraction (LE%) and oxygen consumption (MVO2 ml/min), during 2 rapid atrial pacing tests at equivalent maximal heart rate (HR=147±8 beats/min) during control pacing and after 2.5 mg IV NIC. Results (mean ±SD, *p<0.05 **p<0.01 vs control pacing):

	AoP	HRxAoPx10-^{2}	CI	dp/dt	CSF	MVO2	LE
Control Pacing	105 ±26	174 ±28	2.84 ±.48	1874 ±305	173 ±80	18.7 ±6.5	7 ±7
Pacing +NIC	99 ±15	162 ±20	3.56** ±.65	2143* ±365	204 ±86	20.7 ±6.4	15* ±12

Mean ECG ST depression (lead V5) just after Pacing+NIC was 1±1 mm as compared to control Pacing 1.6±1 mm, p<0.05.

Thus, and in contrast with other calcium antagonists, NICARDIPINE (2.5 mg IV) during pacing in ischemic heart patients produced significant improvements in ventricular function and myocardial metabolism, without lowering myocardial O2 demands. Since CSF and MVO2 remained unchanged, we postulate that NICARDIPINE enhances nutritional flows in ischemic areas.

EFFECT OF NISOLDIPINE ON THE ABNORMAL RESPONSE TO COLD PRESSOR STIMULATION IN PATIENTS WITH SYNDROME X.

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12 patients (pts) with Syndrome X, characterised by typical anginal chest pain, abnormal exercise (ex) ECG's and ex first pass radionuclide angiograms (FPRA), but with normal coronaries, were imaged at rest, and after 1 and 2.5 mins of cold pressor stimulation (CP), before and after the calcium antagonist nisoldipine (nis). No pt had clinical or angiographic evidence of focal coronary spasm. FPRA were performed using gold-195m (t1/2 30.5 secs). Before nis, mean±SD LVEF fell from 61±9% at rest to 55±9% at 1 min of CP, and 56±8% at 2.5 min CP (both p<0.01 vs rest). 10 pts had an abnormal EF response to CP (fall in EF of ≥5%). Nis caused a rise in mean resting heart rate from 83±12bpm to 92±21bpm, and a fall in resting systolic pressure, 145±30mmHg to 136±25mmHg. Both heart rate and systolic pressure rose significantly from rest to both stages of CP before and after nis. Moreover, the CP induced increases in heart rate and systolic pressure from resting levels were not attenuated by nis at either stage. After nis, LVEF was 63±10% at rest, 64±9% at 1min CP and 65±6% at 2.5min CP (p,ns) and only 3 patients had an abnormal response. LVEF was significantly higher at each CP stage compared to values before nis (p<0.001). In conclusion, 1) abnormal response to CP is common in patients with Syndrome X, 2) this response is largely blocked by a calcium antagonist, 3) this effect is not mediated by blocking the heart rate and systolic pressure responses to CP and may be related to inhibition of cold induced coronary vasoconstriction.

INTRAVENOUS NIFEDIPINE VERSUS NITROGLYCERIN IN PATIENTS WITH ANGINA AT REST

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Inappropriate vasoconstriction of coronary arteries - frequently superimposed on pre-existing lesions - may provoke angina at rest responsive to vascular smooth muscle relaxants. Therefore, in 20 patients with angina pectoris at rest either Nifedipine (15 - 30 mg/24 hrs; n = 10 patients, group I) or nitroglycerin (30 - 60 mg/24 hrs; n = 10 patients, group II) was administered intravenously over a 72 hrs observation period in a CCU. Blood pressure (RR, via a femoral cannula), heart rate (HR), pulmonary capillary pressure (PCP), cardiac index (CI, thermodilution technique) and severity of anignal symptoms were recorded on an hourly basis.

Results: In group I patients systolic and diastolic RR fell lastingly (149 ± 10 → 134 ± 13 mmHg, 95 ± 7 → 88 ± 5 mmHg resp.; p < .05), CI rose from mean 3.0 to 3.6 l/min/m^2; p < .02; HR and PCP remained unaffected. In contrast, in group II patients only a transient drop in RR, a reflectory rise in HR, a lasting fall in PCP (14 ± 2 → 8 ± 3 mmHg; p < .02) with unchanged CI was observed. Anginal symptoms were alleviated in both groups 15 - 30 min. after infusion onset and ceased within 2 hours.

We conclude that i.v. Nifedipine acts predominantly through sustained afterload reduction reversing subjective and objective signs of acute myocardial ischemia. This classifies i.v. Nifedipine as an effective alternative to i.v. nitroglycerin in patients with angina pectoris at rest.

SUSTAINED RELEASE VERAPAMIL (360mg) IN ANGINA PECTORIS - EVALUATION OF EFFECT AFTER ONCE-DAILY ADMINISTRATION

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A new preparation of long-acting verapamil (VSR) was given in a dose of 360mg once-daily to 19 patients with reproducible angina and its effects evaluated by treadmill exercise and ambulatory ECG monitoring. The study was double-blind crossover against placebo for 2 weeks, followed by a 4 week period of open treatment with VSR. All drugs were given once-daily and 24-hour ECG monitoring was followed by an exercise test which was carried out 24 hours after the last dose of medication. Blood samples were withdrawn for drug level assay prior to exercise. Exercise time (mean +SEM) increased from 7.4+0.6 min with placebo to 9.6+0.8 min after VSR (P<0.001) and remained at 9.5+0.7 min (p<0.001) after 4 weeks. The mean time to 1 mm ST depression also increased significantly with VSR but there was no significant change in maximal ST depression. Resting and peak systolic BP and double-product decreased significantly with VSR (p<0.05). Analysis of the 24 hour tapes revealed a reduction in the heart rate with VSR particularly between 18 and 24 hours after the last dose. Blood level assays revealed verapamil and norverapamil levels (mean+SEM) of 159.8+68ng/ml and 198+63ng/ml respectively, during the double blind phase and these levels were unchanged at the end of the open period of treatment. Our data suggests that verapamil SR (360mg) is an effective antianginal agent for once-daily administration and this mode of therapy may improve patient compliance.

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LONG-TERM ORAL ADMINISTRATION OF MILRINONE FOR DILATED CARDIOMYOPATHY.

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A randomized double-blind cross-over study was performed in 10 patients with severe idiopathic dilated cardiomyopathy with 14 week treat-ment periods of either 4x10mg Milrinone (M) or Placebo (P), each followed by a 3 week washout period. Radionuclide ventricular studies (ejection fraction EF, peak ejection rate PER, peak filling rate PFR) were performed before and 1 h after 10mg M or P, both at rest and exercise at the beginning and at the end of each 14 week treatment period. Functional capacity (vital signs, symptom score, maximal exercise capacity, maximal oxygen uptake), systolic time intervals, and echocardiographic indices of left ventricular size were monitored throughout each treatment and washout period.

Acute effects:1 h after 10mg M there was a significant increase in PER (1.04 ± 0.7 to 1.32 ± 0.8 EDV/sec.) and PFR (1.18 ± 0.8 to 1.66 ± 1.0 EDV/sec.) as compared to 10mg P (1.23 ± 0.6 to 1.26 + 0.7 and 1.31 ± 0.7 to 1.40 ± 0.8, resp.),a trend to an increased EF (M:18.7 ± 12 to 21.0 ± 13; P: 21.5 ± 11 to 22.1 ± 14) and during exercise a significant increase in EF to 25.3 ± 16 (P: 20.7 ± 14). QS_2I (571 ± 38 to 556 ± 32) and PEP/LVET (0.60 ± 0.13 to 0.58 ± 0.12) decreased, echocardiographic fractional shortening increased (13.9 ± 3 to 15.1 ± 5). There was no change after 10 mg P.

Long-term effects: Within or between the two 14 week treatment periods there was no change in the functional capacity parameters. As compared to the P-periods there was a trend towards deterioration in the hemodynamic parameters during M although after 14 weeks there was still some effect after 10mg M as compared to 14 weeks baseline. No major side-effects occurred during M.

Conclusion: In the dosis tested, oral long-term Milrinone does not improve functional capacity and cardiac performance beyond that provided by standard treatment with digitalis, diuretic drugs and spironolactone in patients with severe idiopathic dilated cardiomyopathy.

HEMODYNAMIC EFFECTS OF NISOLDIPINE IN ACUTE CARDIAC FAILURE AFTER MYOCARDIAL INFARCTION.

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The effect of an intravenous injection of nisoldipine, a new calcium channel blocker with predominantly peripheral vasodilating properties, was studied in 10 patients (pts) with acute cardiac failure (left ventricular enddiastolic pressure $\geq$ 16 mmHg or Cardiac index $\leq$ 2.4 l/min x m^2). 2 µg/kg were administered in 5 pts, 4 µg/kg in another five. The drug was continuously injected over 3 minutes. Heart rate (HR), aortic pressure (AOP), Pulmonary artery pressure (PA), pulmonary wedged pressure (PC), right atrial pressure (RA), cardiac index (CI), total peripheral resistance (TPR), pulmonary resistance (PAR) and stroke volume index (SVI) were recorded for one hour after injection. The data are shown in the table:

		before injection	immediately thereafter	after 60'
HR				
(min^{-1})	2 µg/kg	81.4 ± 7.2	86.2 ± 8.8	77.0 ± 6.6
	4 µg/kg	81.4 ± 18.5	86.2 ± 16.6	82.0 ± 19.6
AOP				
(mmHg)	2 µg/kg	103.2 ± 8.5	95.2 ± 8.3	100.0 ± 5.0
	4 µg/kg	75.4 ± 16.0	62.8 ± 10.4	78.6 ± 28.2
CI				
(l/min m^2)	2 µg/kg	2.6 ± 0.4	3.0 ± 0.3	2.5 ± 0.5
	4 µg/kg	3.1 ± 0.5	3.6 ± 0.8	3.1 ± 0.5
TPR (dyn x sec x cm^{-5})				
	2 µg/kg	1529 ± 423	1233 ± 324	1596 ± 481
	4 µg/kg	967 ± 279	680 ± 195	991 ± 265
SVI				
(ml/m^2)	2 µg/kg	27.1 ± 13.9	35.1 ± 5.0	32.4 ± 5.7
	4 µg/kg	39.1 ± 8.4	42.1 ± 7.6	38.8 ± 6.6

No side effects could be seen in any patient. In all 10 pts a significant change ($p <$ 0.05) could be noted in HR (+ 5.9 %), AOP (–11.6 %), CI (+ 14.3 %), TPR (– 23.4 %), SVI (+ 7.8 %). RA, PC, PA, PAR did not change significantly. Nisoldipine is a potent peripheral vasodilator, which significantly increases stroke volume in patients with cardiac failure.

COMPARATIVE SYSTEMIC AND REGIONAL HEMODYNAMIC EFFECTS OF CALCIUM CHANNEL BLOCKADE AND ANGIOTENSIN CONVERTING ENZYME INHIBITION IN HEART FAILURE.

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The cardiac and peripheral circulatory response to vasodilators with different physiologic mechanisms may be dissimilar. A study was conducted in 10 patients with congestive heart failure in functional class III-IV (New York Heart Association) after administration of 10-30 mg oral nitrendipine, a new calcium antagonist agent, and 12.5-25mg captopril. HR (beats/min), CI (L/min/M^2), mean systemic arterial and pulmonary capillary wedge pressures ($\overline{SAP}$, $\overline{PCWP}$, mmHg), as well as femoral vein oxygen saturation (FVO_2 sat, %) at controls (C_1, C_2) and peak effects were as follows:

	HR	CI	$\overline{SAP}$	$\overline{PCWP}$	FVO_2 sat
C_1	76	1.8	85	23	51
Captopril	73	2.1*	75*	16*	49
C_2	81	1.9	92	21	49
Nitrendipine	80	2.5*+	83*	16*	57*+

*=p<0.05, captopril or nitrendipine vs C; +=p<0.05, nitrendipine vs captopril.

Thus, nitrendipine elicited a greater increase in CI than captopril, while both drugs decreased LV filling pressure similarly. In contrast to captopril, nitrendipine appeared to increase resting skeletal muscle blood flow.

ENALAPRILAT: A NEW PARENTERAL ANGIOTENSIN-CONVERTING ENZYME INHIBITOR: RAPID CHANGES IN SYSTEMIC AND CORONARY HEMODYNAMICS AND NEUROHUMORAL PROFILE IN CHRONIC HEART FAILURE

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Systemic and coronary hemodynamic and neurohumoral effects of a new intravenous angiotensin converting enzyme (ACE) inhibitor, enalaprilat (E, 1.25 or 5.0 mg IV bolus), were evaluated in 10 patients (PTS) with chronic heart failure (ejection fraction 20-40%, 6/10 PTS with ischemic cardiomyopathy) at baseline (B), at 15 and 30 min. and hourly to 6 hrs. Onset of action occurred within 15 min., peak hemodynamic effect within 30 min., and persisted to 4 hrs. There was a significant reduction in mean arterial pressure (MAP, mmHg), pulmonary capillary wedge pressure (PCWP, mmHg), systemic vascular resistance, rate-pressure product (RPP, b/min., mmHgx10^3), and an increase in cardiac index (CI, l/min/m^2). There was no change in coronary vascular resistance, coronary sinus blood flow and average lactate extraction. Three PTS moved from net lactate production at B to uptake at 2 hrs. Plasma renin activity (PRA, ng/ml/hr) increased and aldosterone (A, ng/dl) decreased by 30 min.(*p<.05 vs. B)

	MAP	PCWP	CI	RPP	PRA	A
Baseline	94	27	2.4	12.3	6.2	21.3
30 min	84*	18*	2.8*	10.9*	25.5,p.06	10.7,p.06
2 hrs.	82*	16*	2.5	10.1*	20.1*	7.2*
4 hrs.	76*	17*	2.6	9.6*	-	-

We conclude:1) E is an effective parenteral ACE inhibitor; 2)onset of action is rapid (<15 min) and duration of effect prolonged;3)resting ischemia may be alleviated; 4)the activated renin-angiotensin-aldosterone system responds rapidly to E.

IDENTIFICATION OF PATIENTS WITH SEVERE HEART FAILURE MOST LIKELY TO FAIL LONG-TERM THERAPY WITH CONVERTING-ENZYME INHIBITORS. Milton Packer MD, FACC, Wai Hung Lee MD, Norma Medina RN, Madeline Yushak RN, Paul Kessler MD. Mt. Sinai School of Med, New York, NY

Only 60-65% of patients (pts) with severe heart failure (CHF) improve clinically during long-term converting-enzyme inhibition (CEI), but previous reports have not been able to distinguish responders and nonresponders prior to treatment. We correlated 30 pretreatment variables with long-term response in 134 pts with CHF treated with either captopril (CPT, 75-450 mg/24h, 113 pts) or enalapril (ENL, 20-40 mg/24h, 21 pts) for 1-3 months.

Clinical responders (84 pts) and nonresponders (50 pts) to CEI were similar with respect to age, sex, CHF etiology & duration, serum Na, cardiac index, LV filling and mean arterial pressures, systemic & pulmonary vascular resistances, LV ejection fraction, diuretic dose and plasma renin activity. Responders, however, had a lower serum creatinine (Cr, 1.5 ± 0.1 vs 2.1 ± 0.2 mg/dl, $p<.05$) and a lower mean right atrial pressure (MRAP, 9.9 ± 0.6 vs 14.6 ± 0.9 mm Hg, $p<.01$) than did nonresponders. Stepwise discriminant analysis confirmed that Cr and MRAP were the primary determinants of long-term clinical response.

To determine their interaction, the proportion of responders to CEI is tabulated as a function of pretreatment Cr and MRAP:

	Cr < 1.5 mg/dl	Cr > 1.5 mg/dl
MRAP < 12 mm Hg	37/44 pts (84%)	23/34 pts (68%)
MRAP > 12 mm Hg	14/23 pts (61%)	10/33 pts (30%)

Pts with both a MRAP > 12 mm Hg and a Cr > 1.5 mg/dl had a lower response rate (30%) than did pts in whom only one variable was elevated ($p<0.05$). Pts with low values for both variables had a very high response rate (84%). Long-term hemodynamic effects (by cath) closely paralleled these clinical response rates.

These data confirm experimental work indicating that volume expansion and nephrectomy independently attenuate the response to CEI. As a result, CHF pts who are unlikely to improve during long-term CEI can be identified prior to institution of therapy.

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Pharmacology—Clinical

IV NITROGLYCERIN: INFUSION RATE, PLASMA CONCENTRATION AND HEMODYNAMIC EFFECTS
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Although intravenous nitroglycerin (IV NTG) is in wide clinical use, little is known about the relationship between infusion rate (IR), plasma concentration (C) and hemodynamic effects (HR, BP) over time. We therefore performed acute titrations to maximal tolerated IR (to BP <100 mmHg) and constant 24 hr infusions of maximal IR and placebo in 8 subjects with chronic stable angina. Titration began at 10 mcg/min with 10 mcg/min increments every 10 min x 6 and 20 mcg/min increments every 10 min x6, if needed. Maximal IR ranged from 10-120 mcg/min (m=59 mcg/min or .70 ± .45 mcg/kg/min). IR and C correlated well (r = .79) over 24 hours. Steady state concentration was achieved within 10 minutes. Most subjects showed strong correlations between IR and BP during titration but BP-C, HR-C and HR-IR correlations were weaker. Individual regression lines varied widely. Over 24 hours, IR was constant and C varied little (m=6.54 ± 1.12 ng/ml) and remained unchanged after exercise. HR increase (8 bpm) and systolic BP reduction (20 mmHg) persisted for 24 hours. We conclude that although hemodynamic response to a given IV NTG IR and C varies widely among individuals, the relationship of IR, C and resting hemodynamic effects of a maximum tolerated dose of IV NTG is constant over 24 hours.

TIME-DEPENDING VASOMOTION OF CORONARY ARTERIES FOLLOWING NIFEDIPINE
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In 15 patients (pts) we correlated 1) the diameter changes (Δ-D) of angiographically normal epicardial coronary artery segments (CA) (automated contour detection system, variability ⟨.12 mm), 2) the Nifedipine (Nif) plasma levels (gas chromatography) and 3) the changes of O_2-saturation between coronary sinus and aorta (Δ-AVD-O_2) before and 10, 20 and 30 minutes after 20 mg Nif sublingually. According to the slope of Nif plasma levels pts were subdivided into group A (n = 6 pts) and B (n = 9 pts). Results are (mean values ± SD):

		minutes post Nifedipine		
		10	20	30
plasma levels Nif (ng/ml)	A	21,9±12,5	41,9±21,0	61,7±27,8
	B	14,3± 3,5	22,6± 6,7	28,3±11,0
	p⟨	-	.05	.01
Δ-D (%)	A	6,6± 5,2	10,8± 4,9	15,2± 6,4
	B	-8,1± 7,6	-7,6± 9,6	-3,1±11,8
	p⟨	.001	.001	.01

With constant heart rate pressure product Δ-D and Δ-AVD-O_2 were inversely correlated (r = -.90).

Conclusions: Variability of slope and peak plasma levels after sublingual application of Nif determines the vasodilatory potency of Nif on epicardial and precapillary CA.

NICARDIPINE - A NEW CALCIUM CHANNEL ANTAGONIST: EFFICACY IN STABLE EFFORT ANGINA PECTORIS
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Nicardipine (N) - a new dihydropyridine calcium antagonist - was studied in chronic stable effort angina pectoris (AP): 18 patients, randomly assigned to treatment groups, entered an 8 week trial in which N 10, 20, and 30 mg TID were compared to placebo (PL) in an extended Latin-Square design with a 5 week double-blind phase. Baseline reproducibility was assured by repeat testing. There were no significant differences among group baseline data. Treadmill exercise time (ET) (Bruce protocol) increased from 395±18 sec to 451±21 sec after 30 mg N (mean±SEM; 1 hr data; $p<0.05$). Repeated measures analysis of variance revealed significant differences among groups over time after N: resting rate-pressure product at 1 hr and 4 hr ($p<0.001$); time to onset of AP at 1 hr ($p<0.05$) and 4 hr ($p<0.01$); ET at 1 hr ($p<0.02$) and at 4 hr ($p<0.001$). There were no significant differences in exercise rate-pressure products among groups. The inter-group differences can be attributed to the dosing sequence. A dose-dependent increase in ET was observed, with ET increasing from 395±18 sec to 398±21 sec (10 mg), 409±16 sec (20 mg), and 451±21 sec (30 mg) (1 hr data). A similar effect was seen at 4 hrs. Maximum benefit occurred in the treatment group which received N in 10 mg increments. Two patients did not complete the study due to exacerbation of chest pain and dizziness when assigned directly to 30 mg N TID from PL. These results indicate that N increases ET and produces beneficial hemodynamic effects in AP in a dose-dependent manner. Upward dose titration, beginning with 10 mg TID, produces maximum benefit and fewer adverse effects.

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DIRECT CARDIAC AND PERIPHERAL ACTIONS OF INTRAVENOUS VERAPAMIL.

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The effects of intravenous verapamil on the LV are still controversial. To study this problem, we gave verapamil (0.1 mg/kg bolus followed by 0.005 mg/kg/min) to 10 patients 4 years after coronary bypass grafting. A tip manometer was used to measure AO diastolic pressures (DP), LV systolic (SP) and end-diastolic (EDP) pressures and peak positive dP/dt. Shortening velocity (V) was determined from filmed LV tantalum markers implanted at surgery. Great cardiac vein flow (GCF) was measured by thermodilution and was used to calculate myocardial oxygen consumption ($M\dot{V}O_2$). Results 1 and 15 min after verapamil (*p <0.05 vs control (C); HR = heart rate; TPR = total peripheral resistance):

	C	1'	15'		C	15'
HR	76	82*	73	CI	2.7	2.9*
LVEDP	12	12	14*	TPR	1496	1348*
LVSP	137	120*	126*	V	0.63	0.68
AODP	75	68*	68*	GCF	88	102*
dP/dt	1748	1640*	1570*	$M\dot{V}O_2$	11	13*

Conclusions: Intravenous verapamil in clinical doses results in: 1. peripheral vasodilation and LV unloading; 2. a short-lasting reflex-mediated increase in HR; 3. a progressive fall in dP/dt and a rise in LVEDP, in spite of sustained unloading, due to a direct myocardial effect; 4. no decline in LV pump function due to LV unloading; 5. a rise in GCF accompanied by trivial changes in $M\dot{V}O_2$. Thus, the depressant actions of verapamil on the myocardium are compensated by LV unloading, resulting in preservation of LV pump function.

THE EFFECTS OF TIAPAMIL, A NEW CALCIUM ANTAGONIST, ON EXERCISE INDUCED ANGINA.

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A double blind study of the effects of 4 doses of a new calcium antagonist Tiapamil (T) on exercise (Ex) performance were studied in 10 patients (pts) with coronary disease (CAD) and Ex-induced angina (AP). Maximal treadmill Ex ECGs were performed pre and post randomised, oral doses of 200, 400, 600 or 800 mg T or placebo (P). Ex duration, work load (mets), time to the onset of AP and 1 mm ST-depression were similar pre and post-P, but improved after 600mg or 800mg of T. Ex duration increased from 299±40 secs (mean±SEM) post-P to 399±49 secs post-T 600mg ($p<0.05$) and 416±49 secs post-T 800mg ($p<0.05$). Time to onset of 1mm ST-depression increased from 202±35 secs post-P to 300±48 secs post-T 600mg ($p<0.05$) and 272±51 secs post-T 800mg ($p<0.05$). 8/10 pts were free of AP post-T ≥600mg at similar work loads to peak Ex post-P. 2/10 pts had dizziness and blurred vision after T 800mg. Although T improves Ex tolerance in pts with CAD and AP, its duration of action after a single oral dose is unknown. In another group of 10 pts with AP and CAD, Ex was performed pre and 1, 3, 6 and 9 hours post T 600mg. Results are shown below.

	ExHR	ExDURATION	Work LOAD	ANGINA ONSET
pre	141±23	312±146	5.9±1.6	221±131
1h	143±19	399±118*	7.3±1.3*	310±174*
3h	140±24	360±129	6.6±1.4	299±131
6h	145±24	338±125	6.4±1.3	273±146
9h	142±26	336±155	6.3±1.7	281±172

* $p<0.01$

Thus T 600mg improves Ex tolerance in pts with AP and CAD, with peak effect 1 hour after administration of a single oral dose. T 800mg may produce side-effects.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
Author Present: 9:00AM–10:00AM
Hall D, Georgia World Congress Center
Cardiac Pacing

ANTITACHYCARDIA PACING FOR SUPRAVENTRICULAR TACHYCARDIA: SELECTION OF PATIENTS AND PACING MODES.

Bernd Waldecker, M.D., Pedro Brugada, M.D., Karel den Dulk, M.D. Manfred Zehender, M.D. and Hein J.J. Wellens, M.D., F.A.C.C. Dept. of Cardiology, Univ. of Limburg, Maastricht, The Netherlands.

Antitachycardia pacing (ATP) is increasingly used to terminate paroxysmal supraventricular tachycardia (SVT). To identify patients (pts) amenable to ATP we studied pacing termination of SVT in 111 pts. Mean age was 41 ± 15 years, 62 were male. 76 pts had circusmovement T (CMT) using an accessory pathway, (mean rate 166 bpm) 35 pts had A-V nodal T (AVNT) mean rate 167 bpm). Results: Pacing termination was safe and reproducible in 104/111 pts (94%) irrespective of pts' SVT, sex and age. Similar success rate was found for CMT and AVNT of single (43% vs 41%, p n.s.) and double (60% vs 43%, p n.s.) atrial (A) premature depolarizations (PD). However, in pts with AVNT ventricular (V) PD were less effective than in CMT: 23% vs 53%, $p<0.01$ (1 VPD) and 48% vs 79%, $p<0.05$ (2 VPD). Atrial (91%) and ventricular (100%) bursts terminated CMT as well as AVNT. SVT interrupted by 1 APD or 1VPD were slower than SVT's requiring > 1 APD (157 vs 170/min $p<0.02$) or > 1 VPD (156 vs 173/min $p<0.01$). Antiarrhythmic drugs did not facilitate termination by APD's or VPD's. Induction of atrial fibrillation during pacing (32/111 pts) or other SVT (6/111 pts) was unpredictable from pts' age, sex or clinical SVT but related to number and site of PD's. In pts with CMT and dual AV-nodal pathways pacing induced AVNT in 3/76 pts. Conclusions: 1) Pts with CMT as well as AVNT are amenable to ATP but evaluation by pacing is required before implanting an ATP unit. 2) The efficacy of APD's is SVT rate-related and of VPD's both rate and type of SVT related. 3) Drugs facilitate SVT termination only if they slow SVT-rate.

AUTOMATIC DETECTION OF VENTRICUALR FIBRILLATION WITH CHRONICALLY IMPLANTED PRESSURE SENSORS.

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We studied the feasibility of using RV pressure changes to detect ventricular fibrillation (VF) in five chronically instrumented canines. Permanent pacing leads containing a pressure sensor 3.0 cm proximal to the tip electrode were implanted in the RV apex and the dogs were studied 12-34 weeks post implant. The peak-to-peak amplitude of the pressure (RVP) signal and heart rate were measured before, during and after multiple episodes (3-8) of electrically induced VF in each animal under general anesthesia. An eight beat moving average was used to reduce beat-to-beat variability. Control values (average of 30 sec prior to induction of VF) of RVP during ventricular paced and sinus rhythm were 23.9 ± 13.0 mmHg (range 14.0-44.6 mmHg) for heart rates of 110 ± 30 bpm (range 71-149 bpm). During the first 10 seconds of the 20-30 sec VF episodes, RVP decreased ($P < 0.05$) to an average value of 3.7 ± 2.1 mmHg (range 1.0-6.8 mmHg) for heart rates of 445 ± 31 bpm (range 405-476 bpm). The average percentage decrease in RVP for each dog was 85%, 81%, 93%, 56%, 93%, (82% mean decrease). During VF, the small residual RVP values were associated with atrial activity. The decrease in RVP in one dog of only 56% during VF was always associated with monomorphic ventricular flutter at 434 bpm. After defibrillation, RVP initially (within 5 sec) equaled or exceeded prefibrillation control values.

CONCLUSION: Since large, significant decreases in right ventricular pulse pressure occur during VF in dogs, chronically implanted pressure sensors may be useful for VF detection in an automatic, implantable defibrillator.

EPICARDIAL MAPPING OF THE INITIATION OF VENTRICULAR FIBRILLATION BY SHOCKS DURING THE VULNERABLE PERIOD

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Implantable anti-arrhythmic devices may inadvertently induce ventricular fibrillation (VF) by shocking during the vulnerable period (VP). Little is known about the induction of VF with high energy shocks. Accordingly, we delivered 5 msec shocks of 01 to 20 J via electrodes on the LV apex and RA in 7 open-chest dogs At each energy level, the T-wave was scanned in 10 msec increments while epicardial recordings were made simultaneously from 56 electrodes evenly spaced over both ventricles In no dog did a shock > 5 J induce VF. Immediately following shocks that induced VF, the site of earliest recorded epicardial activation occurred more commonly in the apical half of the ventricles for lower energy shocks and in the basal half for higher energy shocks Two types of epicardial activation patterns were observed following these shocks In 67 cases, activation spread away from the early site in all directions compatible with a focus of micro-reentry or triggered activity (FOCAL), while in 45 cases activation appeared to block unidirectionally on one side of the early site compatible with macro-reentry (UNIDIR)

SHOCK ENERGY	VF EPISODES WITH EARLIEST ACTIVATION		VF EPISODES MECHANISM	
J	AT APEX	AT BASE	FOCAL	UNIDIR
0.01-0.05	14	3	16	1
0.1-0.5	13	42	32	23
1-5	0	40	19	21
Chi Square	P<0.001		P<0.004	

Thus, VF initiated by shocks during the VP appears to arise by more than one mechanism. As energy is increased, the site of earliest activation following the shock tends to move progressively away from the epicardial shocking electrode until an upper energy limit is reached, above which VF does not occur.

SYNCHRONIZED BURST PACING VS. SELF ADAPTING DECREMENTAL OVERDRIVE PACING FOR TERMINATION OF VENTRICULAR TACHYCARDIA.

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Our preliminary experience with self adapting auto-decremental overdrive pacing (DOP) has demonstrated a high degree of efficacy and relative safety for interruption of VT with cycle length (CL)≥280 msec in patients (pts) undergoing programmed ventricular stimulation(PVS). In a comparative efficacy/safety study,we have also shown that this DOP method was superior to antitachycardia pacing methods currently employed for VT including asynchronous overdrive burst (OD) pacing.

In this study we compared in a randomized cross-over fashion DOP to 7 or more stimuli of synchronized OD pacing (ODs)(utilizing the Fisher formula to calculate the burst rate) for induced VT in pts during PVS.The relative efficacy and safety of these two methods were compared in 8 pts with VT-CL ≥ 280msec(CL 280-410msec, Mean 359msec).

Results:	DOP	OD synchronized
Efficacy per pt	8/8(100%)	6/8 (75%)
Efficacy per VT episode	17/18(94%)	10/20(50%)
Acceleration	0/18(0%)	1/20(5%)

Conclusions:1)DOP is more effective in terminating inducible VT when compared to synchronized OD pacing. 2)DOP is safe when applied to well tolerated VT episodes with CL ≥ 280 msec.

PREVENTION OF ACCESSORY PATHWAY MEDIATED TACHYCARDIA WITH A NEW ANTITACHYCARDIA PACEMAKER.

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A-V reentrant tachycardia (AVRT) in patients with an A-V accessory pathway (AP) is often initiated by an atrial premature depolarization (APD) that blocks anterograde in the AP but conducts anterograde through the A-V node. In such cases, initiation of AVRT requires sufficiently slow conduction of the APD through the A-V node to allow reentrant atrial depolarization via retrograde conduction over the AP. P-wave triggered pacemakers that prevent this necessary prolongation of the A-V interval after an APD have been proposed as a means of preventing AVRT, but have been hampered by upper rate limit algorithms of the devices. In 4 patients with an AP whose AVRT could be initiated by APD's, preventive antitachycardia pacing was tested using a new DDD pacemaker with modified upper rate limit characteristics that sensed the APD and then stimulated a ventricular premature depolarization (VPD) with a short A-V interval. Three patients had Wolff-Parkinson-White syndrome. One had a concealed AP capable only of retrograde conduction. In each patient, the range of APD's capable of initiating AVRT was determined using programmed atrial stimulation (PAS). All patients developed sustained AVRT after appropriately timed APD's. PAS was then repeated with the antitachycardia pacing device activated. In all 4 patients, single VPD's initiated within a short A-V interval after sensed APD's prevented initiation of AVRT over the entire range of APD's which previously had initiated AVRT. The mechanism of prevention of AVRT was retrograde block of the VPD in the AP. No patients developed adverse arrhythmias. This technique holds promise for prevention of AVRT in some patients.

OCCURRENCE AND SIGNIFICANCE OF ADDITIONAL REENTRANT TACHYCARDIAS IN PATIENTS WITH AN ANTI-TACHYCARDIA PACEMAKER.

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Medical files and electrophysiological studies were reviewed retrospectively to determine whether reentrant tachycardias (T) other than the T for which the antitachycardia pacemaker (ATP) was implanted, interfered with ATP therapy (21 supra- and 4 ventricular T). At 3 monthly follow-up (mean 21.7 months) T were initiated and terminated non-invasively. During a total follow-up of 543 months, 4418 T occurred spontaneously; 4376 were terminated promptly by the ATP, 10 in <15 minutes, 22 took >30 minutes, failure to terminate T occurred in 10 pts once. Causes were: Defective ATP activator in 2, incorrect use in 1, inadequate antiarrhythmic drug therapy intake in 2, T trigger interval too short after addition of a drug in 1, failure of the programmed ATP pacing mode in 2, and in 2 because of a lead problem. Additional T were seen in 8 pts. In 3, another T (2 atrial, 1 AV-nodal) was identified after ATP implantation. Rate of T changed markedly with a change in reentry circuit due to bundle branch block in 2, WPW syndrome and dual AV-nodal pathways in 1 and 2:1 subnodal block during AV-nodal T in 2. Both clinical and additional T were reproducibly terminated with a single pacing modality in all pts during follow-up evaluation. Conclusion: Additional reentrant T occur frequently(8/25 pts), but do not seem to interfere significantly with the ability to terminate T reproducibly with a single pacing modality.

DETECTION OF ECTOPY BY MEASUREMENT OF VENTRICULAR ACTIVATION SEQUENCE USING TWO ELECTRODES

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The use of 2 ventricular sensing electrodes to determine electrical activation sequence could provide a new method for differentiation of normal from abnormal rhythms by implantable antitachycardia devices. Simultaneous recordings from 2 ventricular sites were obtained during dual chamber pacemaker implantation (5/8 pts), cardioverter-defibrillator implantation (2/8 pts), or programmed electrical stimulation study (1/8 pts). Recordings were made in normal sinus rhythm (NSR) (5 beats each in 8/8 pts), during ventricular tachycardia (VT) (38 beats with 7 morphologies in 3 pts) and during premature ventricular contractions (PVCs) (20 beats with 8 morphologies in 6 pts). Leads were placed transvenously in the right ventricle in 6 pts, and epicardially on the LV in 2. Intervals between the intrinsic deflection of the 2 ventricular electrograms ranged from 0 to 91 ms (mean of 26 ms) during NSR, from 13 to 141 ms (mean of 66 ms) during VT, and from 10 to 72 ms (mean of 40 ms) during PVC's and were reproducible within each pt for each type of rhythm. In all pts the differences in sequence and timing between the dual electrograms in NSR beats vs ectopic beats allowed for the differentiation of normal from abnormal complexes. These differences in each pt ranged from 23 to 210 ms (mean of 81 ms) during VT and from 3 to 89 ms (mean of 44 ms) during PVCs. Fourteen of the 15 ectopic morphologies exhibited $>$ 20 ms difference in timing compared to their corresponding NSR beats. Combined with the appropriate software, multiple ventricular leads may be used by antitachycardia devices to discriminate between normal and abnormal ventricular activity.

POSTURELY INDUCED ACCELERATION OF SUPRAVENTRICULAR TACHYCARDIA AS A CAUSE OF FAILURE OF OVERDRIVE PACE TERMINATION

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Overdrive burst atrial pacing is a common treatment for drug refractory supraventricular tachycardia (SVT). The effective pace termination regimen (PTR) is usually found via electrophysiology (EPS) testing with the patient supine. The purpose of our study was to compare the efficacy of pace termination of SVT in supine vs erect position. SVT was induced by programmed atrial stimulation. The slowest 10-16 beat burst PTR that could terminate SVT 50 times when supine was retested at least 10 times with the patient sitting erect. 3 of 4 consecutive SVT patients tested had acceleration of SVT rate (150 to 170 beats per minute (bpm), 160 to 210 bpm, and 180 to 220 bpm) when erect which negated the efficacy of the previously effective PTR. The PTR in pt 1 was 180 bpm (10 beats) supine, and 220 bpm (10 beats) erect; pt 2-220 bpm (16 beats) supine and none found erect; pt 3-220 bpm (10 beats) supine and 250 bpm (10 beats) erect. Pt 1 received an automatic antitachycardia pacer set at 220 bpm (10 beats) and has had frequent recurrences of SVT effectively terminated in both postures. Pt 2 received a manually activated antitachycardia pacer. She has had occasional failure to terminate spontaneous SVT when erect, and has been instructed to seek supine posture whereupon repeat attempt at termination have been successful. Pt 3 was treated with Amiodarone. Posture induced changes of SVT rate are common, may negate the efficacy of overdrive anti-atrial tachycardia pacemakers, and should be tested for during the preimplant EPS study.

CLINICAL EXPERIENCE WITH A NEW VERSATILE, SOFTWARE BASED, TACHYCARDIA REVERSION PACEMAKER

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To overcome many of the limitations of previous devices, particularly tachycardia recognition and limited tachycardia responses, a new pacemaker (Intermedics Intertach) has been developed and implanted in 7 patients. Tachycardia recognition is achieved automatically using high rate, sudden onset, rate stability or sustained high rate, alone or in combination. Termination may be effected using 1-250 stimuli, which may be rate-related. Extrastimuli or bursts may be scanned with the S1 and S2-Sn intervals being independently programmed. Scanning may start from either preset or from rate-related coupling intervals, and there is also a programmable memory function. Autodecremental bursts ($\pm$ rate-related) are also available. The number and size of scanning (or autodecremental) steps can be programmed, as can the minimum cycle length. Two termination modes, 1^{o} and 2^{o}, may be selected. There is telemetry with full diagnostics, and non-invasive EPS can be performed.

The pacemaker was implanted in 7 patients, aged 23-48, 6 with intra AV nodal and 1 with atrial tachycardia (cycle lengths 250-500, mean 330 ms). All had frequent tachycardias (0.5-20, mean 8 per month) and had failed drug therapy (3-9, mean 6 agents). Only 1 had documented bradycardia. Right atrial pacing was used in all, with 1 patient using only the bradycardia functions - the others use 7 or 8 stimuli in rate-related scanning modes for tachycardia reversion. All 6 experience almost immediate termination of tachycardia without the need for drug therapy. Sinus tachycardias have triggered pacing in 3, but altering the detection criteria has overcome this.

AUTOMATIC IMPLANTABLE DEFIBRILLATORS AND PACEMAKERS - UNIPOLAR VS BIPOLAR.

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The interaction of bipolar and unipolar pacemakers (PM) with automatic implantable cardioverter defibrillators (AICD) was evaluated in 4 pts with dual chamber unipolar PMs and 1 pt with a bipolar single chamber PM.

Amplitudes recorded at implant (in mV, mean and range):

(DVI pacing)	A-spike	V-spike	QRS
AICD large patches	8(4-35)	13(11-15)	9.5(5-14)
AICD epicardial leads	1.9(1-3.2)	14.2(8-21)	18.5(4-10)

Delay from V spike to QRS on AICD leads was variable, mean 80msec (10-150). Inappropriate pacing of unipolar PMs during arrhythmia caused no discharge (DC) in 2 pts in DDD or VVI and delayed DC in 1 in DDD. Appropriate inhibition of 2 dual chamber PMs in VVI during ventricular tachycardia (VT) allowed AICD to DC. Spontaneous DC of AICD was noted in 1 pt in DDD mode not having arrhythmia despite need to satisfy both rate and probability density function. Phonographic recording of AICD audio tone in test mode with simultaneous EKG revealed "triple sensing" of A and V spikes and QRS in pt with long V-spike to QRS delay, particularly after PVC and pause which increase sensitivity of auto-gain sensing amplifier. Change to bipolar PMs revealed no problems in VT for VVI mode. Phono in 1 pt revealed AICD sensing of bipolar pacing spikes at less than the normal pacing output; triple sensing caused DC of the AICD. We conclude that: 1) Unipolar PMs often prevent appropriate DC of AICD because high amplitude of PM spikes blinds AICD to arrhythmia. 2) Bipolar PMs cause less inhibition of AICD, but do not eliminate the problem. 3) V-spike to QRS delay should be measured at time of implant and lead positioned to keep delay less than the AID refractory period (140msec) to avoid DC due to oversensing.

EFFECT OF STIMULUS STRENGTH ON PREVENTIVE STIMULATION OF RECIPROCATING ATRIOVENTRICULAR TACHYCARDIA

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Our previous studies have shown that reciprocating atrioventricular tachycardia (tach) induced from the atria can be prevented from the same site by a short train (T) of extrastimuli delivered right after the tachycardia initiating extrastimulus (S), provided that the length of T exceeds the effective refractory period (ERP) of S by at least 1 stimulus to achieve atrial capture. Amplitude of T stimuli was 2 x diastolic threshold (dthr). The present study was undertaken with 2 objectives: can prevention of tach also be achieved by i) a subthreshold T delivered in the same manner as described above, or ii) by a "superthreshold" T (4 x dthr) delivered completely within ERP of S, i.e. with stimulation modes not intended to yield atrial depolarisation? 9 pts (7 men, 2 women; mean age 38 ± 13 years) with tach due to an accessory AV connection (3 right-sided, 6 left-sided) were studied. Tach (cycle length 312 ± 40 ms) was initiated in all pts from high right atrium with a single S, and in 5 from coronary sinus, with single S in 3 and 2 S in 2, T of 10 stimuli 10 ms apart was delivered at the same site as S and prevention was always successful when T exceeded ERP of S and stimulus strength was 2 x dthr (1.20 - 2.60 V). When stimulus strength was decreased below dthr in the preventive T, atrial depolarisation no longer occured in any pt and tach was not prevented. With T delivered completly within ERP of S and stimulus strength 4 x dthr, tach was also never prevented. – Conclusion: "Superthreshold" stimulation cannot extend ERP of S long enough to prevent tach. Subthreshold preventive stimulation is not possible from the site of tach initiation. It remains to be seen if it will be successful when a subthreshold T can be delivered at the actual anatomic site of the reentry circuit.

Wednesday, March 12, 1986
Poster Displayed: 9:00AM–12:00NOON
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Hall D, Georgia World Congress Center
Hypertension

THE EFFECT OF DRUG TREATMENT FOR HYPERTENSION ON MORTALITY: EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

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Much epidemiological evidence indicates that high blood pressure is an important risk factor for cardiovascular disease mortality. Most long-term randomized controlled trials (RCTs) in mild to moderate hypertension report a substantial reduction in stroke morbidity and mortality but reports of the effects on total and coronary heart disease (CHD) mortality are conflicting. Since many studies have been too small to detect moderate yet important reductions in mortality, we have pooled results from 10 long-term RCTs in predominantly mild to moderate hypertension with published mortality data. These studies reported data from a total of 49,500 patients over an average of 5 years of followup. Mean systolic and diastolic BP in treated patients during followup was 9.3/5.2 mmHg lower than that in control patients. Total mortality in the treated patients was reduced by 11% (95% CI= -18% to -3%); mortality from stroke was reduced by 39% (95% CI= -53% to -21%). Mortality from CHD was 9% lower in treated subjects but this was not statistically significant (95% CI= -21% to +4%). The effect of beta-blockers and diuretics could be compared in two studies (n=15,000); in subjects treated with a beta-blocker total mortality was 7% lower than in subjects treated with a diuretic but this was not statistically significant (95% CI- -23% to +11%). The pooled data demonstrate that antihypertensive drug treatment involving either beta-blockers or diuretics produces a modest though important reduction in total mortality, primarily as a consequence of a reduction in stroke mortality. The data provide weaker evidence of a reduction in mortality from CHD.

DISPARATE HEMODYNAMIC RESPONSE TO MENTAL CHALLENGE AFTER ANTIHYPERTENSIVE THERAPY WITH BETA BLOCKERS AND CALCIUM ANTAGONISTS.

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The hemodynamic response to mental challenge was studied in 40 male, white outpatients with mild essential hypertension before and after randomized treatment with either a beta adrenoreceptor blocker (oxprenolol, 160 mg q.d.) or a calcium channel entry blocker (nitrendipine, 20 mg q.d.). Cardiovascular reactivity was evaluated during two different mental arithmetic tasks before and six months after treatment by measuring systolic and diastolic blood pressure (ultrasonic Doppler device), heart rate (ECG), and stroke volume (impedance cardiography). Patients of both treatment groups had an equal decline in blood pressure and the same pressures at rest. In patients receiving the calcium entry blocker, mental challenge provoked an increase in stroke volume and a decrease in total peripheral resistance equivalent to the reactions without therapy. In contrast, patients on the beta adrenoreceptor blocker reversed the hemodynamic response pattern to a distinct decrease in stroke volume (SV) and an increase in total peripheral resistance (TPR) (Δ SV: -13±3% vs. +25±11%, $p \leq 0.05$. ΔTPR: +11±3% vs. -9±5%, $p \leq 0.05$). In addition, an attenuated heart rate response and a higher increase in diastolic pressure were found in the beta blocker group compared to the calcium entry blocker group (HR: 7 ± 1 vs 18 ± 2 bpm, $p \leq 0.01$; ΔDBP: 16 ± 1 vs 11 ± 1 mm Hg, $p \leq 0.01$). Although both drugs cause an equal fall in BP, beta adrenoreceptor blockers evoke an abnormal hemodynamic response to mental challenge, whereas calcium entry blockers preserve the physiological reactivity pattern of the untreated status.

DOPPLER EVALUATION OF LEFT VENTRICULAR FILLING IN MILD AND SEVERE HYPERTENSION.

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Studies using a variety of techniques have previously shown abnormalities of left ventricular (LV) mass and LV filling in patients with hypertension (HTN). However, the relationship of LV filling changes to the severity of abnormalities in blood pressure (BP) and LV mass is not well-established. Consequently, LV diastolic filling was evaluated by pulsed Doppler echocardiography in 11 patients with treated severe HTN (mean BP: 162/104 mmHg), 22 with mild HTN (mean BP: 147/96) and 66 normal subjects (mean BP: 123/78). Doppler recordings of transmitral flow velocity were made from apical views. Because of the age-relationship of mitral flow velocity, Doppler data were compared after analysis for differences in patient ages. Mitral early diastolic peak flow velocity (PFVE) did not differ in the 3 groups ($p>0.05$). Although mitral late diastolic PFV (PFVA) did not differ between mild HTN patients (mean ± SD: 50 ± 14 cm/sec) and normals (47 ± 11 cm/sec), PFVA was significantly higher in the severe HTN patients (59 ± 14 cm/sec) than in normals ($p<0.03$). Furthermore, early diastolic deceleration was significantly less in the entire HTN group than in normals ($p<0.01$). In the severe HTN patients, mitral PFVA correlated significantly with LV mass ($p<0.05$). However, mitral flow velocity measurements did not correlate with BP. We conclude that Doppler can detect abnormalities of both early and late diastolic LV filling in hypertension. These abnormalities appear to be independent of the level of BP, but some are related to LV mass.

MITRAL VALVE PROLAPSE IN HYPERTENSION: ECHOCARDIOGRAPHIC COMPARISON BETWEEN 133 HYPERTENSIVE AND 230 NORMOTENSIVE CARDIAC PATIENTS.

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We evaluated the prevalence of mitral valve prolapse by two-dimensional echocardiography in 133 patients with hypertension, 65 males, 68 females, age 19 to 87 years. Mitral valve prolapse was diagnosed when systolic posterior or superior arching of the mitral valve leaflets into the left atrium was present in the parasternal long-axis and/or apical four-chamber view. Mitral valve prolapse was seen in one patient with hypertension, this being an 83 year old female with kyphoscoliosis. The 0.75% prevalence in hypertension was significantly lower than the prevalence of 6.1% found in 14 of 230 normotensive patients, 124 males 106 females, age 15 to 97 years ($P<0.001$).

Conclusion: Mitral valve prolapse is rare in hypertension. The low prevalence of mitral valve prolapse in hypertension maybe due to papillary muscle hypertrophy. The effective contraction of the hypertrophied papillary muscles probably pulls the chordae tendinae and mitral valve leaflets away from the left atrium in systole, thus preventing their eversion and prolapse.

SUPRANORMAL LEFT VENTRICULAR PERFORMANCE WITH SEVERE LEFT VENTRICULAR HYPERTROPHY IN ESSENTIAL HYPERTENSION.

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Left ventricular hypertrophy(LVH) previously has been associated with decreased LV performance in essential hypertension(EH). To further examine this relationship we performed radionuclide cineangiography(RNCA) and echocardiography in 105 pts with uncomplicated EH; 10/105 (Group A) had supranormal (≥70%) resting LV ejection fraction [EF] (av 76%; range 71-81%), invariably with normal exercise LVEF[EF_{ex}] (always >74%), while 95 pts (Group B) had normal EF_{ex} (45-70%) with 15/95 having subnormal EF_{ex} (<55%). Group A had higher systolic blood pressure(BP) (EF_{rest} 179mmHg vs 159, $p<.01$), diastolic BP (109 vs 103, $p<.1$), and markedly greater LV mass (276gm vs 184, $p<.01$) than Group B; however, because Group A's marked LVH was concentric, LV dimensions were smaller in systole (2.4 vs 3.0, $p<.05$) and diastole (4.4 vs 4.9, $p<.1$) with resulting larger relative wall thickness (.68 vs .40, $p<.001$) than Group B. Therefore, calculated end systolic wall stress(ESS) was normalized in Group A (43×10^3 dynes/cm^2; normal=46, NS), but was markedly abnormal in Group B (70×10^3 dynes/cm^2, $p<.01$ vs Group A). Although no relationship existed between LVH and LVEF in Group A, EF_{ex} was inversely related to LV mass in Group B ($r=-.50$, $p<.001$). Thus, in EH, progressive LVH and deterioration in LV performance generally are associated, but a subset of pts develops marked concentric LVH in response to abnormal BP, with resulting supranormal LV performance, presumably because of ESS normalization in hypertrophied myocardium.

ATENOLOL BUT NOT ACEBUTOLOL REVERSES LEFT VENTRICULAR HYPERTROPHY SECONDARY TO ARTERIAL HYPERTENSION

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The effects of antihypertensive therapy on left ventricular (LV) hypertrophy are still poorly defined. 13 hypertensive patients, mean age 40 years, were treated for two years with acebutolol (AC, 200-800 mg/die), cardioselective betablocker (B) with intrinsic sympathomimetic activity (ISA), and then, for an other year, with atenolol (AT, 25-100 mg/die), cardioselective B without ISA. They were serially investigated by recording ECG, blood pressure and echocardiogram. The results (mean±SE) are as follows:

	SBP	DBP	HR	EDD	IVST	PWT	MASS	FS	ESS
Control	165	112	69	51	12.5	9.7	154	35	228
	4	2	3	1	0.6	0.2	8	1	10
AC 1y	140**	97**	62*	51	12.5	9.2	150	39*	181**
	5	1	2	1	0.6	0.2	8	2	11
AC 2yrs	141**	98**	64	52	12.6	9.1	155	38*	187**
	4	1	1	1	0.6	0.2	8	1	9
AT 1y	134**	88**¤¤	55**¤¤	52	11.5*¤¤	8.2**¤¤	137*¤¤	40**	183**
	5	2	2	1	0.6	0.2	7	1	9

(SBP, DBP= systolic and diastolic pressure, mmHg; HR= heart rate, b/min; EDD= end-diastolic dimension, mm; IVST, PWT= septal and posterior wall thickness, mm; mass, g/m^2; FS= fractional shortening, %; ESS= systolic stress, dyn.10^3cm^{-2}; * $p<0.05$, ** $p<0.01$ vs control; ¤¤ $p<0.01$ vs AC 2yrs)

AC decreased significantly SBP, DBP, HR and ESS, increased significantly FS. AT reduced ulteriorly DBP and HR, decreased significantly also IVST, PWT and LV mass.

Conclusions: Acebutolol, in spite of its antihypertensive efficacy, did not reduce LV mass. Atenolol, on the contrary, was able to reverse LV hypertrophy, probably for its greater antihypertensive effect and the absence of ISA. Both drugs improved LV systolic function, probably according to decrease of afterload.

ECHO DETECTION OF PRESSURE-OVERLOAD LEFT VENTRICULAR HYPERTROPHY: EFFECT OF CRITERIA AND PATIENT POPULATION

Richard B. Devereux, M.D., FACC, Paul N. Casale, M.D., Isaac W. Hammond, Ph.D., Michael H. Alderman, M.D., Daniel R. Alonso, M.D., John H. Laragh, M.D., FACC. Cornell Medical Center, New York, New York.

To evaluate the performance of M-mode echocardiography for detection of pressure-overload left ventricular hypertrophy (LVH), we tested the sensitivity of sex specific upper limits of echo LV measurements from 225 normals in 31 patients (pts) with necropsy-proven pressure-overload LVH, and determined the prevalence of LVH detected by each echo criterion in 316 employed pts with uncomplicated hypertension (HTN), 100 pts with HTN evaluated in a referral center and 38 hospital pts with moderate to severe (WHO class 2) HTN. Echo measurements were LV mass (LVM), LVM index (LVMI), cross-sectional area (CSA), septal and posterior wall thickness (IVS and PWT), LV internal dimension (LVID) and relative wall thickness (RWT). Prevalences of echo LVH were:

	Necropsied	Patients with Hypertension		
	Patients	Employed	Referral Center	Hospital
n	31	316	100	38
LVM	24 (77%)	57 (18%)	48 (48%)	27 (71%)
LVMI	26 (84%)	60 (19%)	44 (44%)	33 (87%)
CSA	24 (77%)	58 (18%)	41 (41%)	26 (68%)
IVS	16 (52%)	58 (18%)	35 (35%)	24 (63%)
LVID	9 (29%)	15 (5%)	12 (12%)	8 (21%)
PWT	19 (61%)	52 (16%)	33 (33%)	14 (37%)
RWT	15 (48%)	39 (12%)	28 (28%)	9 (24%)

Thus, 1) echo criteria based on LVM are more sensitive than other measurements for detection of necropsy-proven pressure-overload LVH and reveal the highest prevalence of LVH in clinical HTN populations, and 2) the prevalence of LVH in HTN is highly dependent on the population studied.

ECCENTRIC LEFT VENTRICULAR HYPERTROPHY -- A DETERMINANT OF INCREASED VENTRICULAR ECTOPY IN OBESITY.
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Obese patients are prone to develop eccentric left ventricular hypertrophy and are at an increased risk of sudden death (Framingham Study). Cardiac dysrhythmias were evaluated by Holter monitoring in 22 obese subjects (>50% overweight) and compared with those in 18 matched lean subjects (<10% overweight). Arterial pressure was held equal in both groups by study design. Left ventricular dimensions were assessed by M-mode echocardiography. Results were: (mean ± SD)

	Obese	Lean	P
Weight(kg)	102±12	62±5.1	
MAP	116.8±11.2	114.1±13.1	n.s.
PWT	1.22±0.26	1.02±0.08	< 0.02
LVDD	5.46±0.61	4.33±0.42	< 0.001
PVCs/24hr	144±179	8.4±20	< 0.01
PACs/24hr	0.78±1.48	0.58±1.24	n.s.

MAP=mean arterial pressure; PWT=posterior wall thickness; LVDD=left ventricular diastolic diameter; PVCs, PACs=premature ventricular or atrial contractions.
Ten of 18 obese patients had eccentric left ventricular hypertrophy by echocardiographic criteria. Obese subjects with left ventricular hypertrophy (but not those with normal heart) had greater ($p < 0.001$) prevalence of PVCs and graded higher ($p < 0.01$) with regard to Lown's classes than lean subjects. We conclude that the occurrence of eccentric left ventricular hypertrophy increases the risk of ventricular ectopy and more serious arrhythmias in obese patients independent of the level of arterial pressure.

EARLY CHANGES OF CARDIAC FUNCTION AND METABOLISM IN SLOWLY PROGRESSING HYPERTENSION OF THE RABBIT.
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In order to study the early effects of hypertension on the heart we examined isolated hearts from rabbits with slowly developing hypertension of up to 5 months duration after unilateral nephrectomy and renal artery stenosis (one kidney-one clip). Normotensive animals kept under identical conditions served as controls. Mean arterial blood pressure rose from 83 to 111 mmHg ($p<0.01$) in the experimental group, while the ratio of left ventricular weight/body weight was statistically not different (0.206±0.060 vs. 0.239±0.093 g dry/ kg, mean ± SD, N=6) between groups. Although hypertrophy had not yet developed, left ventricular peak systolic pressure of perfused hearts was significantly higher in hypertensive than in normotensive control hearts (155±25 vs. 107±23 mmHg, $p<0.05$, filling pressure = 4mmHg). Furthermore, in hypertensive hearts the peak systolic pressure did not respond to an increase in filling pressure. Functional changes were accompanied by metabolic changes. Rates of glucose utilization were increased and rates of ketone body utilization were decreased in hypertensive hearts. Activities of key enzymes for carbohydrate (hexokinase, lactate dehydrogenase), fatty acid (3-oxoacid-CoA transferase, acetoacetyl-CoA synthase) and Krebs cycle metabolism (citrate synthase, 2-oxoglutarate dehydrogenase) were not different between groups. We conclude that functional and metabolic adaptations of the left ventricle in hypertensive animals antedate the development of hypertrophy. The mechanism for the adaptations does not rest in altered enzyme activities.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #313/314
Doppler Echocardiographic Assessment of Prosthetic Valves

MULTIPLE STENOSIS: IN VITRO CORRELATION OF COLOR DOPPLER/CONTINUOUS WAVE DOPPLER WITH CATHETERIZATION PRESSURES AND LASER DOPPLER
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To assess the accuracy of predicting different pressure gradients in the presence of multiple stenosis of various types (long tunnel stenosis plus one or two discrete stenosis placed in series), color Doppler guided continuous wave Doppler velocities and gradients derived from the Bernoulli equation ($4V^2$) were compared to hemodynamic direct pressure and laser Doppler velocities in a mock laboratory type circulatory system. A plastic disc with variable center holes (50% and 70% obstruction), 5 prosthetic valves of different sizes, and 1.4 cm long plastic tunnels (50%, 70%, 80%, 90% obstruction) were introduced in this system. Heart rate was set at 70 or 120 beats per minute, cardiac output varied from 1 to 7 liters per minute, and the tunnel position was varied from 0 to 4.5 cm downstream and 0 to 1 cm upstream from the valve or disc site. The pressure was maintained at 100 mmHg. The color Doppler guided continuous wave peak velocities ranged from 1.25 to 6.5 m/sec; Doppler derived pressure gradients correlated with direct catheter pressure measurements with a correlation coefficient (r) of 0.98 for peak pressures and 0.97 for mean pressures. These findings were further validated with laser anemometry with r=0.99. In 25 studies done, the highest velocity invariably correlated with the most severe stenosis but was not affected by the coexistent lesser tunnel or disk velocities. Therefore we confirm that in the presence of multiple stenosis of varying severities placed in series at varying distances, the Doppler velocity always reflects the narrowest orifice size.

COLOR FLOW AND CONVENTIONAL DOPPLER ULTRASOUND EXAMINATION OF FLOW BEHIND PROSTHETIC VALVES: AN IN VITRO DEMONSTRATION OF CONCEALED FLOW.
Richard Adamick, M.D., Dennis Sprecher, M.D., David Adams, and Joseph Kisslo, M.D., F.A.C.C., Duke University, Durham, North Carolina.

Conventional pulsed wave, continuous wave (CW) and Doppler (DOP) color flow (CF) studies were conducted in vitro to assess the limitations induced by the presence of a prosthetic valve (PV) in the path of an interrogating beam. Starr-Edwards (silastic and stellite poppets), Bjork-Shiley, and St. Jude's mechanical PV and a Carpentier-Edwards xenograft were sequentially seated in closed position on a stage in a water bath at multiple levels from the DOP source. Behind the seating apparatus, continuous turbulent flow was created by pumping a suspension of microballoons through rubber tubing in two channels, toward and away from the transducer. Without a PV in place, the tubing was readily visualized and DOP flow detected at a peak velocity of 6 m/s (mean velocity 1.5 m/s). No DOP flow could be recorded through the poppets of the Starr- Edwards valves by any DOP technique. There was a significant reduction in the DOP signal (SIG) through the central discs of the Bjork-Shiley and St. Jude's valves and no reduction in the DOP SIG through the cusps of the xenograft. Selectively, CW DOP demonstrated a marked SIG reduction at all velocities with elimination of the higher velocity flows for all disc mechanical PV. There was complete drop-out of the DOP SIG behind the sewing ring for all valves studied. These data indicate that all modalities of DOP are severely and variably limited in the detection of flow behind mechanical PV's due to physical interference with transmission of the DOP SIG. In clinical examinations, the potential for concealed abnormal flow must be recognized whenever the DOP beam traverses a PV.

CONTINUOUS WAVE DOPPLER EVALUATION OF NORMALLY FUNCTIONING NEW PERICARDIAL AORTIC PROSTHETIC VALVES

Jean Philippe Lesbre, M.D., Catherine Chassat, M.D., Jacques Lesperance, M.D., Robert Petitclerc, M.D., Raoul Bonan, M.D., F.A.C.C., Ihor Dyrda, M.D., F.A.C.C., André Pasternac, M.D., F.A.C.C., Martial G. Bourassa, M.D., F.A.C.C., Montreal Heart Institute

No data exist on non invasive determination of maximal velocity, maximal and mean gradients of new pericardial aortic prosthetic valves. Therefore, we studied by continuous-wave-Doppler (CD) and 2 dimensional echo 41 patients (pts) with aortic bioprothesis (B): 20 Carpentier Edwards (CE), 11 Ionescu (IS), 10 Mitroflow (MF). The selection criteria were the following: asymptomatic pts, valvular replacement <4 years, no heart failure, no prosthetic dysfunction on clinical and echo-Doppler grounds. Maximal velocity of aortic flow (V max), maximal (MG) and mean valvular gradients (mG) derived from the Bernouilli equation were measured for each type of B.

Size		CE	IS	MF
19		2.83±0.14	2.67±0.38	------
21	Vmax	2.75±0.58	2.63±0.18	------
23	(x±SD m/sec)	2.23±0.43	2.08±0.38	1.85±0.34
25		2.25±0.35	------	1.5
27			2	1.70±0.14

Size		CE	IS	MF
19		16.4±1.4	14.2±5.0	------
21	mG	17.5±8.2	14.2±0.7	------
23	(x±SD mmHg)	11.5±4.8	9.3±3.8	7.5±3.3
25		10.6±1.4	------	6.2
27		------	9.2±0.7	7.2±1.8

CD-estimated G were very close to published hemodynamic G. There was no correlation between V max, MG and time interval since surgery. V max correlated with B size ($r=-0.71$ - $p<0.01$) and mG differed according to B size (B21 mG versus B23 mG: $p<0.005$ - B19+21 mG versus B23+25 mG: $p<0.0005$). The only significant differences between the 3 B-types were found between CE and MF ($p<0.02$ for V max, MG, mG).
Thus: 1) during the first 4 years after operation, time since surgery does not influence V max, MG, mG 2) B size is the main determinant of these three parameters 3) mG estimated by CD is within the range of reported hemodynamic mG 4) CD is a reliable non invasive method of long-term follow-up of pts with B.

IN VITRO ULTRASOUND FLOW IMAGING THROUGH PROSTHETIC HEART VALVES.

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In response to FDA regulatory responsibilities and recent concern over long term performance of prosthetic heart valves, we have developed an inexpensive laboratory instrument for real-time in vitro imaging of the flow dynamics through prostheses using diagnostic ultrasound imaging without the need for color-flow Doppler. A linear sequential array ultrasound imaging system using 3.5, 5.0 or 7.0 MHz transducers was adapted for use in a Dynatek MV/T1 heart valve visualization chamber which includes a lucite chamber containing a prosthetic input valve and a positive displacement piston pump (0 to 80 pulses/min) operating at normal cardiac pressures of 120/80 mm Hg and a stroke volume of 70 ml. An outflow chamber containing the prosthetic valve to be evaluated and a downstream sinus was cast from acoustically transparent Rho-C rubber (specific gravity of .94 and sound velocity of 1525 m/s). Using this system, the fluid flow through the outflow valve was easily visualized in the real-time ultrasound image using ordinary tap water containing air bubbles as the contrast medium. Alternatively, we imaged the flow properties of simulated blood, fabricated using polystyrene spheres averaging 8 microns in diameter suspended in degassed, distilled water at concentrations approximately equal to the normal hematocrit and blood viscosity. Forward and reverse flow as well as regurgitation, jets and complex circular eddies in the spherical sinus were easily seen using both fluids and the major commercial prosthetic heart valves. The 7.0 MHz ultrasound images showed the highest spatial resolution and greatest target sensitivity to both aerated water and simulated blood at the expense of field of view.

VALUE OF DOPPLER ECHOCARDIOGRAPHY IN ASSESSMENT OF THE FUNCTION OF THE HANCOCK MITRAL VALVE.

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To determine the value of Doppler echocardiography (DE) in assessing the function of the Hancock mitral valve, DE followed within 24 hours by cardiac catheterisation was performed on 19 patients (12 females, 7 males, average age 31 years) who had had Hancock mitral valve replacement from 1 to 7 years (mean 4) previously. The mitral valve gradient was calculated by the modified Bernoulli equation using maximum velocity; mitral valve orifice area (MVOA) was calculated by the equation MVOA=220/pressure half time ($P\frac{1}{2}t$). Data from DE and cardiac catheterisation were compared.

RESULTS: There was strong correlation ($r=0.8$) between DE (range 7.2-22 mmHg, mean 11.4) and catheterisation determined gradient (range 4-26 mmHg, mean 10.5), and also between DE (range 1-2 cm^2, mean 1.44) and catheterisation calculated MVOA (range 0.7-2.5 cm^2, mean 1.45, $r=0.86$); correlation between $P\frac{1}{2}t$ and catheterisation calculated MVOA was good ($r=0.86$).
DE detected mitral valve regurgitation was confirmed by LV angiography in 5 patients, in 2 of whom it was very severe, necessitating surgery. DE detected stenosis (MVOA $\leq$ 1.1 cm^2) in 4 patients was confirmed by catheterisation and 2 required surgery.
CONCLUSION: DE is reliable for (1) estimating Hancock mitral valve gradient and MVOA (2) detecting mitral regurgitation and (3) detecting malfunction of the Hancock valve in both stenosis and regurgitation.

COLOR DOPPLER FLOW IMAGING IN PROSTHETIC VALVES

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Fifty-four patients (pts) with 70 prosthetic valves (PRV) were studied by Color Doppler (CD), 30 tissue valves (VS) in Mitral (M) 19, Aortic (A) 8, Tricuspid (T) 3 positions (P) and 40 mechanical in M 22, A 16, T 2 P. Thirty-five VS functioned abnormally as defined by abnormal motion/increased gradient/presence of significant regurgitation. Forward flow patterns were seen as 1 or 2 jets (J). Visualization of J allowed placing of continuous wave Doppler cursor (DC) in the maximum flow to obtain peak velocity (PV) and if DC could not be aligned parallel to flow, one was alerted to underestimating the PV. Of 35 VS with abnormal function, a narrow jet (less than 50% of orifice size) was seen in 8, with high PV in all. A PRV showed valvular leak (VRL) in 8, one with 2 distinct J. M PRV showed VRL in 10 and VRL and paravalvular valvular leak (PVRL) in 1, some seen as eccentric/thin/multiple J which could have easily been missed on conventional Doppler. T PRV showed VRL and PVRL in 1 and VRL in another. CD also detected associated lesions in 41 pts (17 with normally functioning PRV) AR 6, TR 21, MR 4, PR 10. Prosthetic M inflow and AR could be differentiated by difference in color in oblique short axis view. Major limitation of the system was marked reverberation, specially by mechanical PRV. Thus CD imaging is useful in evaluation of PRV.

Wednesday, March 12, 1986
4:00PM–5:00PM, Room #313/314
Myocardial Perfusion by Contrast Echocardiography

FACTORS INFLUENCING THE PHYSICAL CHARACTERISTICS OF SONICATED MYOCARDIAL ECHO CONTRAST AGENTS

Madeleine Pincu, Ph.D., Ram E. Rajagopalan, M.B.B.S., J. Kevin Drury, M.D, F.A.C.C, Eliot Corday, M.D., F.A.C.C., Cedars-Sinai Medical Center, Los Angeles, CA

Sonicated agents containing microbubbles may permit quantitation of myocardial perfusion by contrast echocardiography, but these agents must first be standardized with respect to factors affecting bubble size distribution, concentration and reproducibility. We thus sonicated 70% sorbitol (S70) at amplitude settings (A) 5 or 6, sonication periods (T) 15 or 30 seconds and sonicator tip immersion depth -- deep or surface. Samples of these solutions placed on a hemacytometer were digitally analyzed using video microscopy, yielding bubble diameters (D) in microns. Results of microscopic image analysis for S70 surface sonication (98 to 870 bubbles) but varying T and A were (mean±SEM, *p<.001 vs A=6, +p<0.001 vs 30"):

Mean Diameter			Concentration ($x10^4$/ml)		
T	A=5	A=6	T	A=5	A=6
15"	14.0±0.4	14.1±1.0	15"	599±48*+	299±45+
30"	14.7±0.4	18.2±1.4	30"	328±75*	152±21

Deep sonication of S70 (at A=5 and T=30") significantly lowered the bubble concentration ($102±40x10^4$/ml, p<0.001) but not the size distribution (13.7±1.3). Samples of S70 (at A=5, T=30 sec) digitally analyzed were compared to visual microscopy and to Coulter counter determinations (all calibrated with solid microspheres of known sizes). The mean number of bubbles measured visually, digitally and by Coulter counting differed markedly (50, 173, 7430 per sample respectively), and diameter measurements (mean ±SD) were 11.9±7.4, 14.7±7.6, 22.3±10.8, respectively. Conclusion: Sonication amplitude, duration and immersion depth significantly affected microbubble concentration but not their size distribution. Divergencies of reported echo contrast microbubble diameter may be due to both instrumentation factors and the sample size analyzed.

A NEW METHOD FOR REAL TIME ASSESSMENT OF REGIONAL MYOCARDIAL PERFUSION

Steven B. Feinstein, MD, Roberto Lang, MD, Edward Geiser, MD, Seth Powsner, MD, Alex Neumann, Kenneth M. Borow, MD, Univ of Chicago, Chicago, IL and Univ of Florida, Gainsville, Fla

There is no precise method for measuring transmural distribution of myocardial perfusion in humans. To study the use of contrast echo as a means of addressing this problem, we developed a canine model (n=6 dogs) for quantification of regional myocardial blood flow. Cross sectional 2D echo in conjunction with injections of sonicated contrast agent solutions were used. ECG gated, volume and pressure controlled aortic root injections of 5–6 ml of sonicated contrast agents [sorbitol (SORB), Renografin–76 (RENO), Dextrose–50 (DEXT)] resulted in increased reflectivity of myocardial tissue by ultrasound imaging. The video images of the myocardium were analyzed by an off line computer equipped with a digitizer and semi–automated edge detection program. This allowed analysis of up to 64 separate myocardial segments. Videodensity vs time curves were generated for comparable regions of interest of the LV endocardium (ENDO) and epicardium (EPI) and fit to a monoexponential function. The lower the myocardial transit time (T1/2) the more rapid the blood flow (i.e. shorter washout of contrast material). Microbubble sizes were assessed by light microscopy. T 1/2 is in seconds (s).

Agent	Bubble Size	T1/2(ENDO)	T1/2(EPI)	ENDO vs EPI
SORB	6 ± 2 μ	2.2±2.2 s	3.5±2.2 s	p<0.05
RENO	10 ± 4 μ	3.3±2.4 s	3.9±2.3 s	p<0.05
DEXT	12 ± 4 μ	5.7±2.3 s	8.1±4.4 s	p=.20

There was a direct correlation between myocardial transit time and microbubble size. With all contrast agents endocardial T 1/2 was shorter than epicardial T 1/2. Only the smallest microbubbles appeared to accurately represent physiologic transit times.

Thus, contrast echo using selected sonicated agents permits real time repetitive assessment of relative ENDO/EPI blood flow. This technique may be suitable for assessing the effects of pharmacologic agents on regional myocardial perfusion.

REACTIVE HYPEREMIA: EVALUATION WITH MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY;

Scott Gage, B.S., Charles G. Vasey, M.D., James C. Dillon, M.D., F.A.C.C., Harvey Feigenbaum, M.D., F.A.C.C., William F. Armstrong, M.D., F.A.C.C.; Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana

Myocardial contrast echocardiography (MCE) accurately localizes regions of non-perfused myocardium but little is known about its characteristics after reperfusion. In this study we determined left anterior coronary artery blood flow (CBF) with electromagnetic flow probes in 8 open chest dogs studied at baseline (n=16), during coronary artery occlusion (CAO) (n=16) and reperfusion (n=30). Aortic root injections of agitated renografin/saline were used for MCE. MCE appearance curves were generated in the involved coronary circulation bed and in two normally perfused myocardial regions. At baseline MCE intensity was equivalent in involved and remote regions; CBF was 23.8 ± 5.9 ml/min and fell to 0 ml/min after CAO. During CAO definite regions of absent contrast effect were seen in all dogs. After reperfusion CBF was 96.6 ± 41.1ml/min and MCE demonstrated an increase in visible brightness in the previously occluded area. Additionally with reperfusion hyperemia MCE peak measured intensity and change from baseline were greater in the involved area than in remote regions (p<.03) or in the baseline study (p<.005). The ratio of peak image intensities in the involved and remote areas (all dogs pooled) correlated with the ratio of hyperemic to basal flow (r=.64, p<.001). Within individual dogs correlation of CBF and MCE peak ranged from .78 to .92. We conclude that reperfusion hyperemia can be both visibly identified and quantified. In individual dogs MCE correlates well with CBF. MCE may be a valuable means of assessing reperfusion and of determining the integrity of the post-occlusion hyperemic response.

EFFECT OF INTRACORONARY INJECTIONS OF SONICATED MICROBUBBLES ON LEFT VENTRICULAR CONTRACTILITY IN HUMANS

Roberto Lang, MD, Kenneth M. Borow, MD, Alex Neumann, Jafar Al-Sadir, MD, FACC, Steven Feinstein, MD, Univ of Chicago, IL

Intracoronary injection of contrast agents used for angiographic visualization of coronary arteries produce significant alterations in LV hemodynamics. However, the effects of echo contrast agents on LV contractility in humans is unknown. Seven patients undergoing elective coronary angiography were studied. 2D targeted m–mode echo and central AO pressures were recorded during injection of standard amount of angiographic (i.e. 7–9 cc of non–sonicated Renografin–76) and echo cardiographic (i.e. 1.5–2.0 cc of sonicated Renografin–76) contrast agents into the left main coronary artery. Each patient received both sonicated and non–sonicated Renografin–76 with the order of injection randomly determined. Microbubble size of sonicated Renografin–76 was 10 ± 4 μ by light microscopy. LV contractility was assessed under control conditions as well as 5 seconds and 15 seconds post intracoronary injection using the load–independent relationship between end–systolic wall stress (σ_{es}) and rate corrected velocity of shortening (Vcf_c). Changes in contractility are shown as ΔVcf_c units from control.

	Non–Sonicated Renografin	Sonicated Renografin
5 sec	−11 ± 2*	0 ± 1
15 sec	−1 ± 1	1 ± 2

(* p<.001 vs control)

An injection of Renografin–76 adequate for angiographic imaging of coronary artery anatomy produced significant depression in LV contractility (p<.001 vs control); recovery occurred within 15 sec post injection. During echo imaging, small amount of sonicated Renografin–76 opacified the myocardium without altering LV contractile state. Thus, in humans, sonicated renografin–76 is a safe echo contrast agent without adverse effects on LV contractility. The volume of contrast material injected rather than the presence of microbubbles appears to be the major determinant of altered LV hemodynamics.

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Wednesday, March 12, 1986
4:00PM–5:00PM, Room #264/265/266
New Detection Techniques: Clinical Applications and Clinical Arrhythmias

CAN ASYMPTOMATIC TELEPHONE ELECTROCARDIOGRAPHIC TRANSMISSIONS SERVE AS A SURVEILLANCE SYSTEM TO DETECT UNSUSPECTED INCREASES IN COMPLEX VENTRICULAR ARRHYTHMIAS?

Craig Pratt, MD, FACC, Donald Slymen PhD, Ann Wierman PAC, Marilyn Francis, RN, LaDean English, LVN, Beth Thornton, RN, Cindy Stone, RN, James Young, MD FACC and Robert Roberts, MD, FACC, Baylor College of Medicine, Houston, TX.

In order to assess the potential of telephone ECG transmissions (TECG) to detect asymptomatic increases in ventricular arrhythmias, we selected 32 patients (pts) with complex ventricular arrhythmias (10♀,22♂, mean age 48 years) with >40 premature ventricular complexes (PVCs)/hour. After >1 year of successful drug therapy, we initiated a one month single-blind discontinuation of antiarrhythmic therapy (placebo pulse). TECGs were tramsmitted 3 times daily (3 minute rhythm strips); 24-hour ambulatory ECG's were done 3 times weekly to verify return of high frequency PVCs. A total of 656 TECG strips were compared to the simultaneous hour of AECG utilizing a model comparable to analysis of covariance. A strong linear relationship was found between PVC frequency on TECG and AECG ($p<001$). TECG strips with >1 PVC reflected >10 PVC/hour on AECG with a sensitivity of 82%, specificity of 90% with 0.9% false positives. In the 21 pts whose arrhythmia frequency returned from <10 PVC/hour to >40 PVC/hour during the 1 month placebo pulse trial, TECG transmissions reflected the increase to >40 PVC/hour within 2 days in all patients (100% sensitivity). Additionally, 6 pts whose arrhythmia frequency did not return to >10PVC/hour by AECG never transmitted a mean of >1 PVC on TECG (despite an average of 60 TECG's/pt); 100% specificity. Thus,TECG effectively uncovers potentially dangerous increases in quantitative arrhythmia frequency, providing daily arrhythmia surveillance.

AUTOMATIC DETECTION OF CARDIAC ARREST RHYTHMS.

Charles M.Jack, M.B., Ernest Hunter, M.B., Terence H. Pringle, M.B., Trevor Wilson, B.Sc., John Anderson, M.Phil. and A.A.Jennifer Adgey, M.D., F.A.C.C., Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland.

During the treatment of successive cardiac arrests, the ECG sensed using disposable pre-gelled defibrillator pads was continuously analysed every 8-18 secs by a microprocessor-based system. The system sampled the ECG digitally and the algorithm looked for absence of an isoelectric segment, irregular energy density spectrum and irregular wave shape. The analysis was displayed visually as ventricular fibrillation (VF) or non-VF and simultaneously the ECG and system's analysis were recorded on tape. Later,the system's interpretation of the rhythm was compared with the ECG record.There were 84 cardiac arrests which occurred in 78 patients(46 male,32 female), aged 14-85(mean 63 yrs).Twenty-nine of the patients had had an acute myocardial infarction. The initial rhythm in 5 of the 84 arrests could not be assessed because of continuous pacing throughout the VF. In the remaining 79 arrests,the initial rhythm was VF in 15 and 14 were correctly detected by the system (sensitivity=93%).Of the non-VF rhythms present initially in the 64 arrests,62 were correctly detected, 2 incorrectly (polymorphic VT) (specificity=97%). Of the 223 episodes (eps) of VF (8-18 secs) 165 were correctly determined by the system,ie 74% sensitivity. When the rhythm was non-VF of 5002 eps,4953 were correctly detected,ie, specificity 99%. Of the 58 eps of VF not detected as VF a change in rhythm to VF occurred during the 8-18 secs analysis in 24 eps.In 16 eps there was low voltage VF (<0.5mV). The accurate determination of cardiac arrest rhythms automatically will allow earlier detection and treatment of cardiac arrest victims outside hospital.

ACCURATE IDENTIFICATION OF ATRIAL ACTIVATION DURING SUPRAVENTRICULAR TACHYCARDIA USING SIGNAL AVERAGED ELECTROCARDIOGRAPHY.

Dennis L. Kuchar MB, Raymond P. Kelly MB, Charles W. Thorburn MB. St. Vincent's Hospital, Sydney, NSW, Australia.

The mechanism of supraventricular tachycardia (SVT) can usually be established without resorting to invasive eletrophysiologic (EP) testing, if the morphology and timing of the P wave can be confidently deduced from surface 12 lead ECG during tachycardia. Unfortunately, this is often difficult to achieve especially when the tachycardia is fast and when the P wave lies within the QRS complex or T wave. Using signal amplification and filtration, the high frequency components of the P wave can be reliably distinguished from the low frequency signals that comprise ventricular repolarization. We prospectively studied 10 patients (pts) with SVT in whom there was disagreement about the identification of the P wave during tachycardia and in whom the mechanism of SVT was subsequently established by EP study. During tachycardia, high fidelity tracings were recorded from 3 orthogonal leads (X, Y, Z) then amplified (100 x), signal averaged for 100-200 beats (to reduce noise levels to < 1uV) and filtered (40-250Hz). The resultant ECG was compared to one taken during sinus rhythm.

Results: Two pts with orthodromic atrioventricular tachycardia using an accessory pathway had clearly defined P waves following the QRS in the ST segment or coincident with the T wave. Two patients with atrial tachycardia and 3 with atrial flutter with 2:1 block had discrete atrial signals which allowed a correct diagnosis to be made on the basis of established criteria for P wave rate and morphology. In 3 pts with AV nodal reentrant tachycardia, atrial activity was deduced to lie partially or wholly within the QRS complex when it could not be seen elsewhere in the cycle.

Conclusion: The use of signal processing provides a means of accurate identification of the P wave during tachycardia and leads to more confident noninvasive bedside diagnosis of the mechanism of SVT.

HEART RATE VARIABILITY PATTERNS IN STABLE AND REJECTING CARDIAC TRANSPLANT RECIPIENTS.

Kenneth E.F. Sands, Leonard S. Lilly,M.D., F.A.C.C., Frederick J. Schoen, M.D., Gilbert H. Mudge, Jr., M.D., Richard J. Cohen, M.D., Ph.D. Brigham and Women's Hospital, and Harvard-MIT Division of Health Sciences and Technology, Boston, MA.

Power spectrum analysis is a technique used to characterize beat-to-beat heart rate variability, which normally reflects ongoing autonomic modulation of cardiac function. We used power spectrum analysis to study heart rate variability longitudinally in 8 patients, maintained on cyclosporine A therapy, within 15 months after orthotopic cardiac transplantation, and in 6 normal subjects. Total heart rate variability in clinically stable transplant recipients was reduced 98.9% compared to normal subjects ($p<0.001$). In three transplant recipients, total heart rate variability was observed to abruptly increase more than 30-fold; immediately subsequent endomyocardial biopsies in these patients demonstrated the onset of myocardial rejection. Heart rate variability during the period of rejection did not demonstrate the characteristic spectral peaks seen in normal subjects, but rather a broad-band pattern.

We conclude: (1) heart rate variability is greatly reduced in stable transplant recipients; (2) Increased broad-band heart rate variability may be a significant non-invasive marker of acute myocardial rejection in cardiac transplantation patients treated with cyclosporine.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #260/261
Electrocardiographic Manifestations of Ischemia

DIURNAL VARIATION IN OCCURRENCE OF TRANSIENT MYOCARDIAL ISCHEMIA DOCUMENTED BY COMPACT ANALOG ANALYSIS OF HOLTER RECORDINGS: DIFFERENCES BETWEEN CHRONIC STABLE AND PRINZMETAL ANGINA.

Koonlawee Nademanee, M.D., F.A.C.C., Vanida Intarachot, R.N., Jo Ann Hendrickson, B.S., Martin Josephson, M.D., F.A.C.C., Bramah N. Singh, M.D., Ph.D., F.A.C.C., Wadsworth VA Hospital, Los Angeles, CA.

Patients(pts) with chronic stable angina (CSA) experience symptoms on exertion during daytime; those with Prinzmetal angina(PA) usually spontaneously and at night. Ambulatory Holter monitoring(AHM) especially with compact analog(CA) analysis has shown that in both CSA and PA, most episodes of transient myocardial ischemia(TMI) are silent. Whether silent TMI has diurnal variation (DV) is not known. Thus, TMI from AHM obtained on no therapy in 65 pts with angiographically or ETT-documented coronary artery disease (CAD) - 56 with CSA and 9 with PA - was analyzed by CA technique. In PA mean (±SD) number of TMI episodes was 19.5±10(total 176), mean duration of TMI was 3.5±3 min./episode (longest episode 16 min.). In CSA, mean number was 4.5±2 episodes (total 514), mean duration 11±15 (longest 256) min./episode.

Diurnal pattern of TMI episodes:

	6A.M.-Noon	Noon-6P.M.	6P.M.-Midnight	Midnight-6A.M.
CSA	198 (39%)	217 (42%)	72 (14%)	27 (5%)
PA	35 (20%)	44 (25%)	51 (29%)	46 (26%)

Conclusions: 1) Compared to CSA, TMI episodes in PA were shorter in duration ($p<0.01$) and more frequent ($p<0.01$). In CSA, most TMI episodes occur during waking hours. 3) There is no DV in TMI in pts with PA. 4) These findings are of therapeutic and diagnostic significance.

MONITORING OF MYOCARDIAL ISCHEMIA BY EPICARDIAL ELECTROGRAMS DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

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Monitoring of myocardial ischemia during percutaneous transluminal coronary angioplasty (PTCA) is important to ensure safety during balloon inflation and to detect possible complications. To aid prompt detection of ischemia, local unipolar epicardial electrograms (Ep-EG) were recorded during PTCA in 14 patients from the tips of teflon-coated PTCA guide wires positioned distal to stenoses to be dilated. Surface limb and precordial electrocardiographic leads (ECG) chosen to reflect likely areas of reversible ischemia during PTCA were recorded simultaneously. 8 patients had stenoses of the anterior descending, 5 of the circumflex and 1 of the right coronary artery. 12/14 patients developed marked ST segment elevation (ST↑) in Ep-EG during balloon inflation that disappeared after deflation. Of these 12, 10 also had angina that began and subsided concurrently with EP-EG ST↑ whereas 2 had reversible Ep-EG ST↑ without angina. 2/14 patients had fixed Ep-EG ST↑ unrelated to balloon inflation, reflecting prior myocardial infarction and aneurysm formation in PTCA territory. Reversible ST changes in the ECG during balloon inflation occurred in only 6/14 patients, 5 having ST↑ and 1 ST depression. These 6 patients all had ST↑ in Ep-EG that appeared earlier during inflation and was of much greater magnitude than ST changes in ECG. We conclude that myocardial ischemia during PTCA can be detected easily with Ep-EG and with greater sensitivity than the surface ECG. Ep-EG may reveal local ischemia even when angina is absent. Finally, Ep-EG may clarify the nature of chest pain during balloon inflation or during suspected complications.

ABOLITION OF HOLTER-DETECTED SILENT MYOCARDIAL ISCHEMIA FOLLOWING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

Martin A. Josephson M.D., F.A.C.C., Howard S. Lewis, M.D., Koonlawee Nademanee, M.D., F.A.C.C., Vanida Intarachot, R.N., Kristine Coyle, B.A., Bramah N. Singh, M.D., Ph.D., F.A.C.C., Wadsworth VA Hospital, Los Angeles, CA.

Percutaneous transluminal coronary angioplasty (PTCA) is effective treatment for exercise-induced ischemia. The effects of PTCA on silent ischemia(SI) detected by Holter monitor(HM) are unknown. Forty-six patients undergoing PTCA had 24 hour HM before and after (n=38) successful PTCA. Defining a significant stenosis as ≥70% diameter reduction, 32 patients had single, 12 double, and 2 triple vessel Coronary artery disease(CAD). All patients had ischemia on ECG during either thallium exercise scintigraphy (n=35) or during angina (n=11). PTCA markedly reduced or eliminated exercise-induced ischemia in all patients. SI was detected in 11 patients (24%) undergoing PTCA. Nineteen % of single, 33% of double, and 50% of triple vessel CAD patients had HM SI. There were 3.5 SI episodes per patient with a mean duration of 8.4 min/episode. Successful PTCA completely abolished SI in these patients ($p^2.05$). Two patients without SI pre-PTCA had 1 SI episode following successful PTCA; one of these patients had 3 vessel CAD and only 1 vessel PTCA.

Conclusions: 1)HM SI is infrequent in patients with 1 or 2 vessel CAD undergoing PTCA. 2) Successful PTCA abolishes HM SI episodes. In patients with HM SI 3) HM provides an additional method for assessing efficacy of PTCA.

CIRCADIAN VARIATION OF TRANSIENT MYOCARDIAL ISCHEMIA.

Michael B. Rocco, M.D., Joan Barry, Stephen Campbell, M.D., Elizabeth G. Nabel, M.D., George S. Rebecca, M.D. and Andrew P. Selwyn, M.D., FACC. Brigham and Women's Hospital, Boston, MA.

Patients with angina may notice increased symptoms in the mornings. To test the hypothesis that a circadian variation of myocardial ischemia exists and is not due to differences in activity or myocardial demand, 33 patients with positive exercise tests and proven coronary disease underwent 68 days of continuous 24 hour frequency modulated ST-segment monitoring off medications to determine the frequency (F) and duration (D) of ischemic ST-segment depressions (STD) (≥ 1mm at 80 msecs and ≥30 secs duration). Detailed diaries of activity were kept. The mean waking time was 6:34 AM ± 55 min. 256 episodes of STD occurred in 24 patients (73%) with a duration of 1 to 253 mins. (median=5.0). The 24 hour distribution for F and total D was:

	12 AM-6	6 AM-12	12 PM-6	6 PM-12
F:	42(16%)	98(38%)	58(23%)	58(23%)
D:	330(14%)	1151(47%)	363(15%)	604(24%)

The distributions of F and D in these 4 time periods were significantly different ($p=0.03$ and $p=0.01$). 13 of 33 patients had STD throughout both AM and PM waking activity. There were no significant differences in physical activity and heart rate at onset of STD or change in heart rate 1 min prior to onset comparing the 6 hours after waking (peak STD) and 6 hours before bed. A circadian rhythm of STD exists with peak activity during the first 6 waking hours. This does not appear to be due to differences in physical acitivty or simple measures of myocardial demand and may represent differences in coronary flow (supply). The medical therapy of coronary disease may have to consider this surge of ischemic activity in the morning.

THE SIGNIFANCE OF PAINLESS ST SEGMENT DEPRESSION ASSESSED BY AMBULATORY PULMONARY ARTERY PRESSURE MONITORING
Richard D Levy MB BS MRCP(UK), Leonard M Shapiro MD MRCP, Christine Wright SRN, Lorna Mockus SRN, Arshed A Quyyumi MB BS MRCP, Kim M Fox MD MRCP
The National Heart Hospital, London, England.

In order to study the significance of painless ST segment depression in patients with coronary artery disease (CAD), we have developed a system for recording the ambulatory pulmonary artery pressure using a transducer tipped catheter with a simultaneous frequency modulated electrocardiogram and a miniaturised tape recorder. In 17 patients with CAD studied for 650 hours there were 40 episodes of angina recorded during the day. In two episodes of angina the ECG and PA diastolic pressure (PADP) did not change. In 9 a significant increase in PADP preceded the onset of ST depression, in 10 the reverse occurred and in the remainder the changes were simultaneous. Peak ST depression and peak PADP occurred simultaneously. ST depression was more prolonged (2.3mins) than the PADP elevation (1.4mins). The increase in PADP on exertion (86% range 33-237) was greater than at rest (63% range 23-128). In these patients 40 episodes of daytime painless ST depression were also recorded, the haemodynamic and ST segment changes being similar to those of the painful episodes. The increase in PADP was lower in the painless (67%) than in the painful episodes (86%). Two episodes of PADP rise occurred in the absence of ST changes. In 13 episodes of nocturnal ST segment depression the changes were similar to those of the daytime episodes other than a smaller rise (50%) in PADP. Thus ambulatory pulmonary artery pressure monitoring has shown that painless ST segment depression differs from painful ST depression only in the magnitude of the haemodynamic response.

ST SEGMENT RESPONSE TO CORONARY OCCLUSION: DEPENDANCE ON COLLATERAL FUNCTION
Robert G. Macdonald, M.D., James A. Hill, M.D., F.A.C.C., Robert L. Feldman, M.D., F.A.C.C., University of Florida, Gainesville, FL.

To assess the relationship between ST segment response to transient coronary occlusion and coronary collateral function, ECG and coronary and LV hemodynamic responses were evaluated in 23 patients (pts) undergoing proximal LAD PTCA. ECG leads I, II, V5; LV, Ao and distal coronary (cor) pressures (p); and great cardiac vein flow (GCVF, thermodilution) were measured. During a 1 min. LAD occlusion all pts had angina; 11 had ST elevation (group I) and 12 had ST depression (group II). Magnitude and direction of ST response were consistent with repeated occlusions. ST elevation was never preceded by depression during any LAD occlusion.

Before PTCA, LAD diameter reduction was 68±14% (mean±SD) in group I vs 83±12% in group II ($p<.01$). Angiographically visible filling of the LAD via collaterals was present in no pts in group I vs 5 pts in group II ($p<.05$). During LAD occlusion peak LV filling p (19±6 vs 21±8 mmHg, group I vs group II), heart rate (78±18 vs 77±12 b/min) and mean AoP (108±20 vs 109±13 mmHg) were similar in both groups. Group I pts, however, had lower distal cor p (25±7 vs 39±14 mmHg, $p<.05$) and residual GCVF (35±9 vs 51±21 ml/min, $p<.05$) and higher calculated collateral resistance (2.5±.6 vs 1.6±.7 mmHg/ml/min, $p<.05$), compared to group II pts.

Thus, estimates of myocardial oxygen demand were similar in both groups. In contrast, in pts with ST depression pre-PTCA stenoses were more severe; visible collaterals were more common; and hemodynamic parameters of collateral function were superior. Collateral function was an important determinant of direction of ST response and presumably magnitude of ischemia during coronary occlusion.

Wednesday, March 12, 1986
4:00PM–5:00PM, Room #260/261
Clinical Problems Due to Ventricular Malfunction

ECHOCARDIOGRAPHIC INVESTIGATION OF THE HEMODYNAMICS OF WEIGHTLESSNESS.
Michael W. Bungo, M.D., F.A.C.C., John B. Charles, Ph.D., Jeanne Riddle, R.N., JoAnn Roesch, R.N., David A. Wolf, M.D., and M. Rhea Seddon, M.D., NASA - Johnson Space Center, Houston, Texas.

Extensive ground-based simulations of spaceflight utilizing bedrest or water immersion have been performed. Little data, however, has been acquired on humans during actual spaceflight. A commercial ADR 4000SLC ultrasound machine was modified and placed in a Space Shuttle locker during mission 51D. M-mode and 2-D sector images of the heart were obtained from four crewmembers daily for the duration of the seven day orbital flight. These data were compared to resting supine values acquired preflight and at selected intervals postflight. Right ventricular dimension was found to be 35% decreased throughout the period of weightlessness and returned to baseline after flight. Left ventricular volume index (LVDVI) was 20% increased on the first day of flight and 15% decreased thereafter when compared to preflight. Stroke volume tracked LVDVI. Mean blood pressure and heart rate were both 20% increased during weightlessness. Increases in both diastolic and systolic pressure contributed to the rise of mean pressure. After a 85% rise in cardiac index the first day, values returned to preflight levels for the duration of the mission, but were again 59% elevated during the postflight recovery period. Elevated trends in cardiovascular work and total peripheral resistance were noted throughout flight. Recovery from 7 days in space appeared to require a week of re-exposure to Earth's gravity.

ENHANCED LEVELS OF CIRCULATING ATRIAL NATRIURETIC PEPTIDE DURING VENTRICULAR PACING IN HUMANS
Michael J. Osborn, M.D., F.A.C.C., Stephen C. Hammill, M.D., F.A.C.C., John C. Burnett, Jr., M.D., Department of Medicine, Mayo Medical School, Rochester, MN

Mammalian atrial tissue possess specific atrial granules which synthesize and release atrial natriuretic peptide (ANP) which participates in the control of arterial pressure and renal sodium excretion. The mechanism of release of ANP in man is unclear. The present study was designed to test the hypothesis that acute elevation of right atrial pressure (RAP) results in acute release of ANP. Studies were performed in two groups of patients undergoing diagnostic electrophysiologic investigation. Measurements were obtained of plasma ANP employing a radioimmunoassay to alpha-human ANP during atrial pacing (atrial rate 144±9 bpm) in 6 patients and ventricular pacing (ventricular rate 130±8 bpm) in 5 patients.

	RAP mmHg	ANP pg/ml
	Atrial Pacing (n=6)	
Resting	2.2±0.5	46.0±6.1
Pacing	2.5±0.2	35.1±4.7
	Ventricular Pacing (n=5)	
Resting	0.8±0.5	75.5±11.6
Pacing	4.8±1.1*	162.4±28.5*

*p<.02

These studies are the first to establish in man that acute elevation of right atrial pressure, produced by ventricular but not atrial pacing, results in acute elevation of circulating atrial natriuretic peptide. These studies support the hypothesis that atrial pressure is an important determinant of atrial natriuretic peptide release.

ALTERED PLATELET FUNCTION IN PATIENTS WITH SEVERE CONGESTIVE HEART FAILURE. Jeanne M. Riddle, Ph.D., Syed M. Jafri, M.D., Surdara B.K. Raman, M.D., and Sidney Goldstein, M.D., F.A.C.C., Henry Ford Hospital, Detroit, MI

We assessed platelet function in 22 patients with severe congestive heart failure (CHF) and 33 normal subjects of comparable ages. The platelet count per mm^3 was determined. Platelet surface reactivity (ability of platelets to spread and aggregate contacting a foreign surface) was evaluated using a transmission electron microscope. Aggregometry studies used collagen, adenosine diphosphate, epinephrine and arachidonic acid as inducers in platelet rich plasma. Release factors (platelet factor 4 and beta-thromboglobulin) were evaluated using radioimmunoassay. The presence of circulating aggregates was also investigated.

The mean number of circulating platelets was 243,700 (196,800, 335,600/mm^3). A hyperactive platelet response (>27% of spread type platelets and/or > 81 aggregates) was found in 64% of patients with CHF. Mean % of spread type platelet and average number of aggregates were 42% and 67 compared to 14% and 45 found for normal ($P<0.001$). On average aggregation with all of the inducers was normal (50-55%). The mean PF4 level was 19.3ng/ml (normal 4.5-11.9ng/ml and B-TG was 124.1ng/ml (normal 25.4-67.1ng/ml). No circulating aggregates were detected. Subgroups of patients with conditions known to alter platelet function such as gout, diabetes mellitus, coronary artery disease, CVA and those receiving antiplatelet drugs were analyzed separately. None of the tests of platelet function were significantly different in the subgroups compared to CHF patients without the platelet modifying states. Our studies indicate that platelet function is abnormal in patients with CHF. The increased platelet relativity found might account for the increased incidence of the thromboembolic events in CHF patients.

SUCCESSFUL THROMBOLYSIS DOES NOT PREVENT VENTRICULAR DILATATION AFTER MYOCARDIAL INFARCTION IN MAN
S.E. Warren, M.D., H.D. Royal, M.D., W. Grossman, M.D., J.E. Markis, M.D., and R.G. McKay, M.D., Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, Massachusetts.

Left ventricular (LV) dilatation (DIL) after myocardial infarction (MI) has been reported to occur commonly, but whether this can be prevented by thrombolysis is uncertain. We studied this question in 29 patients undergoing thrombolytic therapy for acute MI. Streptokinase was used as the lytic drug in 23 cases and urokinase in 6. The mean time from chest pain onset to reperfusion was 4.9±1.0 hours. Radionuclide ventriculography was done within 24 hours of MI, at 2 weeks, and at 6±4 months, and a geometric technique was used to derive LV end-diastolic volume (EDV). Patients were identified as showing dilatation if they had ≥20% increase in LVEDV from baseline at either 2 weeks or 6 months post-MI. Thrombolysis outcomes, occlusion sites, and presence or absence of dilatation are listed for left anterior descending (LAD) and right (RCA) coronary arteries.

	Thrombolysis successful, n = 16		Thrombolysis unsuccessful, n = 13		
	Occlusion site		Occlusion site		
	LAD	RCA	LAD	RCA	Graft occlusions
LV DIL	6	3	3	2	1
No LV DIL	3	4	3	4	

Incidence of LV DIL, thrombolysis successful: 9/16
Incidence of LV DIL, thrombolysis unsuccessful: 6/13 } p=NS
LV dilatation after LAD occlusion: 9/15; after RCA: 5/13
Overall incidence of LV dilatation after MI: 15/29

Conclusions: 1. Thrombolysis relatively late (4.9±1.0 hours) in the course of MI did not influence development of LV dilatation; 2. LV dilatation following MI was a frequent event, occurring in about half of patients, and was more common after LAD occlusion than after RCA occlusion.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #360/361
Supraventricular Tachycardias

ATRIOVENTRICULAR NODAL TACHYCARDIA-HOW MUCH NODE IS NECESSARY?
John M. Miller, MD, Mark E. Rosenthal, MD, Joseph A. Vassallo, MD, Mark E. Josephson, MD, FACC. University of Pennsylvania, Philadelphia, PA.

Atrio (A)-Ventricular (V) nodal reentrant tachycardia (T) is presumed to be an intranodal circuit. To determine if the entire AV node is required for T, we analyzed 21 patients with AV nodal reentrant T by pacing A, then V, at or near (within 15 beats/minute) T rates. Criteria suggesting the presence of AV nodal tissue between the T circuit and A (upper common path) were: during A pacing, an A-His interval>A-His in T; or paced AV Wenckebach at a rate<T rate. Criteria suggesting the presence of AV nodal tissue between the T circuit and His (lower common path) were: during V pacing, His-A interval>His-A in T; or paced VA Wenckebach at a rate<T rate. Criteria were met if paced Wenckebach rates, A-His or His-A intervals were >10 milliseconds different from those during T. Criteria for lower common paths were met more frequently (13/18 attempts) than upper common paths (6/18 attempts; $p<0.03$).

Path	Criterion	# of Cases	Difference in Pacing vs T Rates
Upper	A-His(A pace)>A-His (T)	4	58±46 ms
	Wenckebach rate<T rate	2	38±13 beats/min
Lower	His-A(V pace)>His-A (T)	11	26±22 ms
	Wenckebach rate<T rate	2	38±37 beats/min

In sum: 1) the AV nodal T circuit is completely intranodal, with nodal tissue between the T circuit and both A (upper common path) and His (lower common path), 2) using these criteria, lower common paths can more frequently be demonstrated than upper common paths in AV nodal T, 3) properties of such upper and lower common paths in the AV node may influence the ability to penetrate the T circuit for initiation, resetting, or termination of T with rapid pacing or extrastimuli.

PREVENTION OF REENTRY BY PRE-EXCITATION OF AV JUNCTIONAL REENTRANT CIRCUITS: EFFICACY AND ELECTROPHYSIOLOGIC MECHANISMS.
Rehan Mahmud, MD, FACC, Mohammed Jazayeri, MD, Patrick Tchou, MD, Stephen T. Denker, MD, FACC, Masood Akhtar, MD, FACC, Univ. of WI Mt. Sinai Med Center, Milwaukee, WI.

The concept of prevention of reentry (Re) by "pre-exciting" areas of conduction delay and/or unidirectional block (i.e., the AV node (AVN) and/or accessory pathway (AP), was tested in 6 patients (pts) with clinical AV nodal Re (N=3) or W-P-W syndrome and orthodromic tachycardia (N=3). The zone of Re was defined by atrial (A) drive (A_1-A_1) followed by premature stimuli (A_2) at progressively shorter A_1-A_2 interval (control method). Then the A_1-A_1 drive was replaced by ventriculo-atrial (V-A) sequential drive in order to "pre-excite" (or depolarize earlier) the AVN and/or AP, prior to delivery of A_2. The degree of pre-excitation was increased by programming longer V-A intervals (0-100 msec).

Results: V-A sequential pacing decreased the tachycardia (SVT) zone, longer VA intervals produced greater decrease in zone of Re and in 5/6 pts abolished SVT altogether. The prevention of Re by A_2 was related to a) decrease in conduction time in "slow" pathway, i.e., failure to achieve "critical" AVN delay (from 274 ± 49 to 190 ± 47 msec: $P<.02$). b) a shift in site of block in retrograde pathway, as Re failed to occur despite achievement of critical AVN delay at short A_1-A_2 interval and c) a decrease in antegrade effective refractory period of AP.

Conclusions: 1) Simultaneous "pre-excitation" of areas of conduction delay and unidirectional block produce functional changes in Re circuits which are effective in preventing Re 2) Our data indicates that the concept of prevention of Re by pre-excitation may be applicable to both small and large clinical Re circuits.

ENTRAINMENT OF CIRCUS MOVEMENT TACHYCARDIA BY VENTRICULAR PACING:SIGNIFICANCE OF SUPRA AND INFRA-HIS BUNDLE COLLISION

Liaqat Zaman,M.D.,Agustin Castellanos, M.D., F.A.C.C.,Richard G. Trohman, M.D.,Richard M. Luceri, M.D.,Alberto Interian,Jr.,M.D.,and Robert J. Myerburg, M.D.,F.A.C.C., University of Miami,Miami, Fl.

Entrainment of circus movement tachycardia(CMT) by ventricular pacing(VP) is usually difficult to demonstrate due to the lack of an apparent retrograde His bundle electrogram(H') during VP.We studied 7 patients with atrioventricular accessory pathways and analyzed 18 episodes of induced CMT with clearly apparent H' during attempted entrainment by VP.Conventional criteria for entrainment were achieved in all CMTs, i.e., capture of all elements of CMT at VP cycle length and resumption of CMT on cessation of VP. To determine the supra or infra-His(H) level of collision of successive VP impulses,H'-H' during VP was compared with the cycle between H' from the last VP impulse and H of the first CMT beat (H'-H).H'-H'=H'-H in 9 CMTs (317±62 ms)-group A. In contrast, the remaining 9 CMTs showed H'-H > H'-H'(310±34 vs231±27, Δ H=79±25 ms)-group B. Mean CMT cycle length in group A=339±53 and in group B=273±25 ms. Mean VP cycle length in group A was 315±58 ms (92±3% of CMT cycle length) and 231±27(84±3% of CMT) in group B. The first VP impulse was delivered as late as possible in the CMT cycle ;74-97(89±7)% of CMT cycle length in group A, and 81-93(87±3)% in group B. In conclusion:1)H'-H prolongation relative to H'-H' in group B CMTs reflects supra-H (AV nodal) collision of successive VP impulses during entrainment;2)infra-H collision in group A occurred due to longer VP cycle length;and 3) the later may be a more accurate method to demonstrate entrainment, because the former may result in CMT termination and reinitiation during VP.

INCIDENCE AND DIAGNOSTIC VALUE OF QRS ALTERNANCE DURING WIDE QRS TACHYCARDIA.

Mohammad Shenasa, M.D., Ph.D., Réginald Nadeau, M.D., F.A.C.C., René Cardinal, Ph.D., Mohammad A. Sadr-Ameli, M.D., Pierre Pagé, M.D., F.A.C.C. Sacré-Coeur Hospital, Université de Montreal, Canada.

QRS alternance during narrow QRS tachycardia is reported to be specific for the participation of accessory pathway (AP) in the retrograde direction. We examined occurrence of QRS alternance during sustained monomorphic wide QRS tachycardia of either right (R) or left (L) bundle branch block (BBB) configuration in 148 patients (pts) in whom the site of origin of tachycardia was determined during electrophysiologic studies. 79 pts had ventricular tachycardia (VT) and 69 pts had wide QRS supraventricular tachycardia (SVT) as follows: 33 with intra A-V nodal tachycardia and 36 pts had SVT due to participation of AP in the retrograde direction. Of the latter pts, 9 had right-sided AP and 27 had left-sided AP. QRS alternance occurred in 13 (16%) of pts with VT independent of QRS configuration (RBBB vs LBBB) and QRS duration. QRS alternance did not occur in any of pts with intra A-V nodal tachycardia of either RBBB or LBBB morphology. QRS alternance observed in 6 (8.6%) pts with SVT due to AP in the following manner. In those with left-sided AP, QRS alternance never occurred during SVT-LBBB but occurred during SVT-RBBB (5 cases). In pts with right-sided AP, QRS alternance occurred only in 1 pt during SVT-LBBB. Conclusions: QRS alternance occurs during wide QRS tachycardia either due to VT or SVT. Therefore, it is not helpful in differentiating VT from SVT. In pts with APs, QRS alternance may be seen only in counterlateral SVT-BBB to the AP site.

MECHANISTIC DISTINCTION BETWEEN LONG R-P' REENTRANT TACHYCARDIAS: DIFFERENTIAL EFFECTS OF ADENOSINE AND VERAPAMIL.

Bruce B. Lerman, MD, Mark Greenberg, MD, Luiz Belardinelli, MD, T. Duncan Sellers, MD, FACC, John P. DiMarco, MD, PhD, FACC. University of Virginia, Charlottesville, Virginia

Long R-P' supraventricular reentrant tachycardias (SVT) often demonstrate decremental conduction properties in the retrograde limb of a circuit. The anatomic substrate of the retrograde limb can be quite variable since it may be comprised of the AV node or represent extranodal tissue with AV nodal-like properties. Differential electrophysiologic effects between nodal tissue and extranodal accessory pathways with decremental conduction properties have not been previously reported. To elucidate the physiologic substrate of this tissue, electrophysiologic effects of adenosine and verapamil were examined in 5 patients (pts) with fast-slow AV nodal reentry (F-S), and 2 pts with accessory pathways having decremental conduction properties. Verapamil (10 mg), an agent which decreases Ca^{++} conductance in the AV node, terminated all episodes of F-S tachycardia in the retrograde limb but had no effect on the 2 pts with decremental accessory pathways. Adenosine (3.8 ± 0.5 mg), a nucleoside which enhances K^+ conductance and hyperpolarizes supraventricular tissue, terminated SVT in the retrograde limb in all pts.

Therefore retrograde accessory pathways with decremental conduction properties may be distinguished from AV nodal tissue by their differential responses to verapamil and adenosine. This suggests that K^+ conductance rather than the inward calcium current is a major determinant of the conduction properties of decremental retrograde accessory pathways in the basal state.

ATRIAL MAPPING OF HUMAN ATRIAL FLUTTER DEMONSTRATES REENTRY IN THE RIGHT ATRIUM

Brian Olshansky, M.D., Ken Okumura, M.D., Richard W. Henthorn, M.D., F.A.C.C., Andrew E. Epstein, M.D., F.A.C.C., Vance J. Plumb, M.D., F.A.C.C., Albert L. Waldo, M.D., F.A.C.C., University of Alabama at Birmingham, Birmingham, Alabama

Reentry in the right atrium has been demonstrated during atrial flutter (AFl) induced in dogs with sterile pericarditis. Here we demonstrate a similar finding in 8 patients with spontaneous AFl, 4 with coronary artery disease, and 4 with other conditions. All underwent electrode catheter mapping of the right atrium during AFl, mean cycle length 245±28 ms. Bipolar atrial electrograms were recorded from the right atrial catheter utilizing a grid of 30 equally spaced sites, with catheter position confirmed by 3 independent observers. A reference electrode catheter was placed in the coronary sinus (7 patients) or in the His bundle position (1 patient). The sequence of right atrial activation was determined during stable AFl off antiarrhythmic medications. In all patients with AFl, the mapping sites from the free wall of the right atrium were activated in a cranio-caudal direction and the septal sites were activated in a caudo-cranial direction. In 4 patients, atrial electrograms were recorded throughout the entire AFl cycle. An area of slow conduction was always present in the inferior right atrial free wall. In the other 4 patients, atrial electrograms were not recorded during 40±8% of the AFl cycle, due to a missing interval in the inferior right atrial free wall. Double and fractionated atrial electrograms were always recorded in the posterior-inferior portion of the free wall of the right atrium during AFl, but were either normal or of low amplitude during sinus rhythm. These data demonstrate: 1) the similarity between AFl in the dog model and in humans; 2) that a reentry loop can be identified during AFl in the right atrium; 3) that during AFl, abnormal atrial electrograms and an area of slow conduction exist in the inferior right atrium.

Wednesday, March 12, 1986
4:00PM–5:00PM, Room #360/361
Ventricular Arrhythmias—Electrophysiologic Testing II

PROGRAMMED ELECTRICAL STIMULATION IN HYPERTROPHIC CARDIOMYOPATHY – SPECIFICITY AND SENSITIVITY OF DIFFERNT STIMULATION PROTOCOLS

Klaus-Peter Kunze, M. D. Karl-Heinz Kuck, M.D., Manfred Geiger, M.D., Walter Bleifeld, M.D., F.A.C.C., Dept. of Cardiology, University Hospital Eppendorf, Hamburg, West Germany

The value of programmed electrical stimulation (PES) in identifying patients with hypertrophic cardiomyopathy (HC) at risk for syncope (S) or sudden death (SD) is under investigation. To determine the sensitivity (SE), specificity (SP), and prognostic value (PV) of two different stimulation protocols (STIM) consisting of 2 and 3 ventricular extrastimuli (VES), respectively, we analysed the data obtained during PES of 26 consecutive pts with HS (13 men, 13 women, mean age 45 years). Four pts had a history of S, 2 had had cardiac arrest (CA) due to ventricular fibrillation (VF). STIM included atrial as well as RV and LV stimulation. Endpoint of STIM was induction of sustained (sus) ventricular tachycardia (VT) or VF. Pts were defined as pts at risk, if sus VT or VF could be initiated during PES. During the follow-up period of 32 ± 5 months pts with S or CA were treated with oral amiodarone (400 mg/day) independently from the results of PES according only to clinical data. All other pts received either calcium antagonists or beta blockers. RV and LV stimulation with maximally 2 VES resulted in VF in 3/26 pts. Two of these 3 pts had a history of S or CA. Using 3 VES at the same sites of stimulation VF was initiated in another 7 of the remaining 23 pts, of whom none had a history of S or CA. Sus VT was never induced. During clinical follow-up no pt suffered from S or CA. Thus only pts with a previous history of S or CA were considered to be pts at risk. Based upon these data, SE, SP, and PV of each STIM for the recognition of pts at risk for S or CA were: STIM using 2 VES: SE 20 %, SP 95 %, PV 66 %, STIM using 3 VES: SE 0 %, SP 65 %, PV 0 %. – Conclusion: PES using STIM with 3 VES should not be performed in pts with HC because of its lack of sensitivity and specificity. A STIM using 2 VES needs further evaluation.

RESULTS OF A STANDARDIZED VENTRICULAR STIMULATION PROTOCOL IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY.

Annette Geibel,M.D., Pedro Brugada,M.D., Manfred Zehender,M.D., Ivo Kersschot,M.D., Hein J.J. Wellens, M.D.,F.A.C.C. Dept. of Cardiology, Univ. of Limburg, Maastricht, The Netherlands.

Hypertrophic cardiomyopathy (HCM) is frequently associated with the occurrence of spontaneous complex ventricular arrhythmias (VA)or sudden death. The relevance of VA induced during programmed electrical stimulation (PES) in these patients (pts) remains uncertain. 18 pts with HCM were studied with a standardized stimulation protocol. Three pts had been resuscitated from documented (D) ventricular fibrillation (VF-group), 2 pts had a history of syncope (Syn) and 2 pts had D sustained monomorphic ventricular tachycardia (DSMVT-group), 11 pts had no D VA (No-VA-group). PES consisted of 1-2 extrastimuli (EX)(part-1) and 3 EX (part-2) during sinus rhythm (SR) and pacing at 100, 120 and 140/min from the RV-apex; part-2 also included pacing with increasing rates (IR) in the atrium and the RV-apex. Part-2 was used in 11 pts when part-1 failed to induce a SMVT or VF. Results: In 12/18 pts (67%) repetitive ventricular responses and in 10/18 pts (56%) a sustained VA was induced. Part-1 induced a SMVT only in 2 pts with DSMVT and VF in no pt. Part-2 induced SMVT in 1 pt without DSMVT, and a polymorphic VA requiring DC-shock in 7/11 pts (64%) (3/3 pts with VF, 2/3 pts with No-VA, 1/2 pts with Syn, 1/2 pts with SMVT). 1/3 VA induced during part-1 and 8/8 VA induced during part-2 required DC-shock for termination. Conclusions: 1) In pts with HCM, 1-2 EX can easily identify pts with D SMVT, with a low risk for DC-shock, 2) 3 EX and IR frequently induce non-specific polymorphic VA requiring DC-shock for termination, 3) pts with HCM without D SMVT are rarely inducible by PES to a SMVT.

PROGNOSIS IN SUDDEN DEATH SURVIVORS WITHOUT INDUCIBLE VENTRICULAR ARRHYTHMIAS.

David Wilber, MD, Beth Kelly RN, Hasan Garan, MD, Jeremy Ruskin, MD, FACC. Massachusetts General Hospital, Boston MA.

Thirty-two patients who survived out-of-hospital cardiac arrest not associated with acute myocardial infarction had no inducible ventricular arrhythmias (IVA) during subsequent programmed ventricular stimulation. Of 21 patients with obstructive coronary artery disease (CAD), 12 had 3 vessel disease and 9 had remote myocardial infarction. The remaining patients had valvular disease (3), dilated cardiomyopathy (2), mitral valve prolapse (1), or no structural heart disease (5). The mean left ventricular ejection fraction was .48 ± .19, and was similar in those with and without CAD.

Six patients had recurrent cardiac arrest (RCA) during follow-up ranging from 3-88 mo: 3 with CAD, 2 with valvular disease, and 1 with no structural disease. Ejection fraction was > 50% in 3 patients with RCA. Of 11 patients treated with antiarrhythmic agents, 2/9 treated for spontaneous high grade ventricular ectopy and 0/2 treated for atrial arrhythmias had RCA. In CAD patients, 0/4 treated with revascularization and 1/10 treated with beta adrenergic blockade had RCA. Two patients died from heart failure and 2 of noncardiac causes. Actuarial incidences were:

	1 year	3 years	5 years
RCA	13%	17%	25%
All cardiac deaths	13%	21%	29%
All deaths	16%	28%	35%

Conclusion: Sudden death survivors without IVA during electrophysiologic testing, including those with normal ventricular function, remain at moderate risk for RCA. The potential protective effect of beta blockade/ coronary revascularisation requires furthur study.

RISK OF ARRHYTHMIA RECURRENCE IN VENTRICULAR TACHYARRHYTHMIA PATIENTS WITHOUT INDUCED SUSTAINED ARRHYTHMIAS.

Charles D. Swerdlow, M.D., F.A.C.C; Roger A. Freedman, M.D.; Jan Peterson, R.N.; Debra Clay, R.N.; Stanford University, Stanford, CA.

We studied 59 patients (pts) with sustained (>30 sec) ventricular tachycardia (VT, 27 pts) or ventricular fibrillation (VF, 32 pts) in whom programmed stimulation induced ≤ 15 repetitive ventricular complexes. In all pts, programmed stimulation included 3 extrastimuli from 2 ventricular sites at 2 cycle lengths and burst pacing. Pts were treated with antiarrhythmic drugs (33 pts), surgery (6 pts), or devices (4 pts); 16 pts had no therapy. During followup of 2.2+1.5 yrs, 13 pts had an arrhythmia recurrence: sudden death in 7, aborted VF in 4, and sustained VT in 2. At 1, 2, and 3 years, the actuarial incidence of arrhythmia recurrence was 15+5%, 17+5%, and 23+6% and that of sudden death was 6+4%, 15+6%, and 21+8%. Prior myocardial infarction (MI) was the only independent predictor of arrhythmia recurrence (p<.02) and sudden death (p=.05): At 2 yr, 36+12% of 18 pts with MI and 8+4% of 41 pts without had arrhythmia recurrence; 24+12% with MI and 3+3% without had sudden death. None of the 9 pts with > 70% coronary stenosis but no MI had arrhythmia recurrence after antiischemic therapy. Possible arrhythmia-precipitating conditions were present during all arrhythmias in 14 pts (antiarrhythmic drugs, K^+<3.0, ischemia, or perioperative state), but did not predict freedom from arrhythmia recurrence (p=.52) or sudden death (p=.81). Age, sex, LV ejection fraction, use of LV programmed stimulation, clinical arrhythmia type (VT or VF), use of chronic antiarrhythmic therapy, or number of induced ventricular complexes did not correlate with arrhythmia recurrence or sudden death. **Conclusions:** In this group of pts, prior MI predicted arrhythmia recurrence and sudden death. The risk of arrhythmia recurrence was low in coronary pts without MI who received antiischemic therapy. The risk did not correlate significantly with possible arrhythmia-precipitating conditions or the duration of induced nonsustained VT up to 15 complexes.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #366/367
Evaluation of the Heart by NMR

MONITORING OF CARDIAC ALLOGRAFT REJECTION WITH MAGNETIC RESONANCE IMAGING.

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To determine the reliability of magnetic resonance imaging in the diagnosis of cardiac allograft rejection, 12 patients were imaged 10-14 days, 25-30 days, and 45-60 days following surgery on a 0.15T resistive system. Endomyocardial biopsies were obtained within 24 hrs of imaging in all cases. Rejection was defined as the presence of both a cellular infiltrate and myocytolysis.

Results were as follows:

	Rejection(n=4)		Non-rejection(n=8)	
	T1	T2	T1	T2
Early imaging (10-14 days)	490±17*	61±4*	500±19*	62±4*
Late imaging (25-60 days)	500±18*	62±5*	350±13	35±4
Control	350±12	35±4	350±12	35±4

*p<.05 vs control

Thus, magnetic resonance imaging does not appear capable of separating early rejection accurately from the tissue changes that occur following graft harvesting and implantation, but has promise for subsequent monitoring of patients beginning 3-4 weeks after surgery.

ESTIMATION OF SIZE AND LOCALIZATION OF MYOCARDIAL INFARCTION BY MAGNETIC RESONANCE IMAGING.

Jennifer A. Johns M.B.B.S, F.R.A.C.P., Tsunehiro Yasuda M.D., Herman K. Gold M.D., F.A.C.C., Robert C. Leinbach M.D., F.A.C.C., Donald L. Johnston M.D., Thomas J. Brady M.D., Robert E. Dinsmore M.D., F.A.C.C.
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Magnetic resonance imaging (MRI) has shown regional increase in myocardial signal intensity following acute myocardial infarction (MI). The aim of this study was to determine the ability of MRI to accurately estimate the size and location of MI. We studied 19 patients with MI, 14 of whom received thrombolytic therapy with either tissue plasminogen activator or streptokinase, within 6 hours of onset of MI. All patients underwent repeat coronary arteriography and left ventriculography (LVA) 10 days post-MI. Multi-slice spin echo MRI at TE=30/60 msec, followed by single-slice imaging at TE=60 msec at 0.6 Tesla was performed 5-20 days (mean 9) post-MI. Image planes oriented to the true short axis of the left ventricle were used and multiple gated systolic images from aortic valve to apex were obtained, allowing precise comparison of left ventricular segment location on MRI with LVA. The length of infarcted myocardium on MRI was measured by multiplying the number of contiguous image slices showing increased signal intensity by 1.5cm (i.e. slice thickness). This was then compared with the location and length of akinesis (cm) on LVA.

Infarct location on MRI agreed with angiographic location in all cases. There was good correlation of MRI infarct length with angiographic akinesis (MRI length = 0.85 LVA akinesis + 0.6, r=0.85, p < 0.001), indicating that MRI has potential for accurate estimation of infarct size and localization in humans.

DISSOCIATION BETWEEN H-1 NMR T_1 AND WATER CHANGES WITH MYOCARDIAL ISCHEMIC INSULT

R.C. Canby, M.E.E., R.C. Reeves, M.D., F.A.C.C., W.T. Evanochko, Ph.D., and G.M. Pohost, M.D., F.A.C.C.
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Contrast produced by differences in regional proton relaxation times provides the potential to assess the extent of myocardial infarction (MI) using NMR imaging. Previous studies have shown that T_1 is prolonged in acute MI, and these prolongations have been wholly attributed to increases in tissue water content. No study has focused on total ischemia, where regional myocardial blood flow (RMBF) is zero, and tissue water content should not increase, although the insult is severe. The left anterior descending coronary artery and collaterals to a region of the left ventricle were ligated in 8 dogs for four hours, and bulk T_1 values of myocardial biopsy samples were measured at 20 MHz. T_1 values (.70±.03s) with severe flow reduction (SR, RMBF≤2% of preocclusion flow) were not significantly different from T_1 values (.69±.02) with no flow reduction (NR, RMBF>50%), while the wet weight to dry weight ratios (W/D) of SR (4.75±.28) were larger than NR (4.44±.17, p<.01). T_1 values (.78±.05s) with moderate flow reduction (MR, 2%<RMBF≤50%) were significantly higher than NR (p<.0001) and SR (p<.0001); the W/D of MR (4.93±.29) were also greater than NR (p<.0001), but were not greater than SR. The data suggest that contrary to previous beliefs the behavior of T_1 changes in MI is not solely determined by tissue water content. Furthermore, clinical imaging of T_1 relaxation times may provide a means for characterizing the severity of ischemic insults; we anticipate that T_1-weighted images of severe myocardial infarction might demonstrate a doughnut pattern with an area of increased T_1 in the peripheral zone and no increase in the central zone.

A NEW PARAMAGNETIC CONTRAST AGENT FOR MAGNETIC RESONANCE IMAGING OF EXPERIMENTAL MYOCARDIAL INFARCTION.

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University of Texas Health Science Center at Dallas, Dallas, TX.

A paramagnetic contrast agent which enhanced contrast between infarcted and normal myocardium with high specificity could improve the sensitivity and specificity of magnetic resonance imaging in the detection of myocardial infarction. The phosphonate complex is known to localize in regions of infarction. Hence, a Gadolinium phosphonate complex (Gd-P) was prepared and compared to a non-specific paramagnetic contrast agent Gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) in a model of infarction. In 24 dogs the left anterior descending coronary artery was occluded for 2 hours, released, and each dog was given 0.34, 0.034 or 0.0034 mM/kg Gd-DTPA or Gd-P intravenously. Following one hour of reperfusion the hearts were excised and imaged. In relatively T1 weighted spin echo images (SE 500/28) the ratio of infarcted to normal myocardial signal intensity was as shown below:

	0.34 mM/kg	0.034 mM/kg	0.0034 mM/kg
Gd-DTPA	1.39±0.11	1.21±0.08	1.08±0.04
Gd-P	1.38±0.12	1.50±0.09	1.29±0.10
	p=NS	p<0.005	p<0.01

At lower concentrations contrast was better with Gd-P than with Gd-DTPA. These results suggest that Gd-P localizes more specifically to regions of infarction than Gd-DTPA. Agents such as Gd-P may be useful in the detection of infarction by magnetic resonance imaging.

PROTON MAGNETIC RESONANCE FOR THE DETECTION OF VIABLE MYOCARDIUM WITHIN A REPERFUSED ISCHEMIC RISK AREA

D. Douglas Miller, M.D., Howard L. Kantor, M.D., H. Thomas Aretz, M.D., Donna Lutrario, B.S., Arno Villringer M.D., Thomas J. Brady, M.D., Robert D. Okada, M.D., F.A.C.C., Massachusetts General Hospital, Boston, MA.

To determine whether proton magnetic resonance (MR) can detect viable myocardium in reperfused infarctions (MI), 7 dogs had 3 hrs of left anterior descending coronary occlusion followed by 1 hr of reperfusion. Mannitol (12.5gm/50ml) was infused at 15.3 ml/min for 15 min before and after release to promote myocardial salvage. Microsphere myocardial blood flow (MBF) was measured at control(c), peak occlusion(o) and 15 min of reperfusion(r). Biopsies were obtained before sacrifice from the normal, central and border ischemic zones for electron microscopy (EM). After MR imaging in a small-bore (1.4T) superconducting magnet, excised hearts were stained with T.T.C. Spectrometer (20MHz) T1 and T2, % water content($\%H_2O$) and MBF were calculated for 34 normal, 57 central and 27 border endocardial segments for correlation with EM and T.T.C. Segments with the lowest MBFo(7% of MBFc = 0.06±.07 ml/min/gm) had the highest T1 (623±30ms) and T2 (48±6ms) and were predominantly (>90%) T.T.C.(-). In these MI segments, T1 and T2 correlated with MBFo (r=.52; p<0,001), and rose exponentially as MBFo approached zero. T1 (593±14ms) and T2 (43±5ms) were lower (p<0.001) and unrelated to MBFo in normal segments. Segments bordering the MI were moderately ischemic (46% of MBFc=0.33±.07 ml/min/gm) and >90% T.T.C.(+). MBFo, T1 (607±20ms) and T2 (46±5ms) in border segments differed from MI and normal values (p<0.05). T2 correlated linearly with MBFo in these segments (r=.41; p<0.05). $\%H_2O$ content did not differ between normal, border and infarcted segments (77±3 vs 78±5 vs 79±3%). All segments showed mannitol effect (i.e. decreased T1, T2, and $\%H_2O$) compared to 9 untreated hearts (p<0.05). EM of MI segments confirmed the ultrastructural changes of irreversible injury (grade 3-4+), while border zone changes were less marked and reversible (grade 0-1+). T1-dependent inversion recovery and T2 spin-echo images had smaller abnormalities than control dogs in the distribution of T.T.C.(-) segments.
We conclude that although significant differences in blood flow, T1 and T2 can be measured in vitro, viable ischemic myocardium does not produce sufficient intrinsic MR contrast to be imaged at 1.4T.

DYNAMIC STUDIES OF CARDIAC MOTION AND FLOW WITH A FAST MULTIPHASE MRI TECHNIQUE.

Ir. Pieter van Dijk, Ir. Peter van der Meulen, Roderic I. Pettigrew, Ph.D., M.D., Rainer Blümm, M.D., Wayne Dannels, B.S., and Joost Doornbos, Ph.D., Philips Medical Systems, Best, The Netherlands.

The low signal intensity of fast flowing blood in conventional spin echo (SE) imaging makes the assessment of cardiovascular flow abnormalities difficult. In addition, the dynamic studies which can be obtained using variable slice order SE techniques have limited temporal resolution, since these are typically based on images of a slice obtained at 5-6 phases of the cardiac cycle. We report our experience with a new fast imaging sequence which uses gradient echos, combined with short echo times and small angle excitation pulses, to produce positive contrast for flowing blood. In addition, with ECG gating, images of a single slice at typically 16 phases of the cardiac cycle can be obtained in only 4 minutes. Cine display of these images provides high temporal resolution studies in which the dynamics of blood flow, and to a lesser extent the heart wall motion, can be evaluated. Initial clinical assessment suggest particular utility of this technique in the differentiation of slow flowing blood from thrombus, identification and assessment of false lumen flow in aortic dissection, and the evaluation of pulmonary hypertension and flow patterns in congenital heart disease. This technique also holds promise for fast flow quantification and MRI angiography.

Wednesday, March 12, 1986
4:00PM-5:00PM, Room #366/367
Exercise Testing and Myocardial Infarction

THE ST/HR SLOPE IDENTIFIES THREE-VESSEL CORONARY DISEASE AFTER REMOTE BUT NOT AFTER RECENT MYOCARDIAL INFARCTION

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The rate-related change in exercise ST segment depression (ST/HR slope) has been shown to accurately identify 3-vessel (3v) coronary disease (CAD) in patients (pts) with stable angina (SA), but the method is inaccurate after recent (<3 weeks) Q-wave myocardial infarction (MI). Although some pts with SA have had prior MI, the possible effect of remote (>8 weeks) Q-wave MI on ST/HR slope accuracy in pts with chest pain has not been examined. To quantify and compare the ability of an ST/HR slope >6 μV/beat/min to identify 3v CAD in pts with recent and remote MI, we evaluated 107 pts studied by the Bruce protocol in whom ST/HR slope analysis was limited to leads aVF, V5, and V6. The 58 pts with SA, including 17 with remote Q-wave MI, were similar to the 49 pts with recent MI with respect to age and peak exercise heart rate. In pts with SA and no prior Q-wave MI, an ST/HR slope >6 had a sensitivity (sens) of 92% (11/12), specificity (spec) of 97% (28/29), and positive predictive value (ppv) of 92% (11/12) for 3v CAD. In SA pts with remote MI sens was 83% (5/6), spec 91% (10/11), and ppv 83% (5/6). After recent MI, spec was preserved at 95% (39/41), but sens was only 37% (3/8) (p<0.025 compared with sensitivity in SA patients) and ppv 60% (3/5). These findings suggest that discordant reports of the accuracy of the ST/HR slope in pts with CAD may be partly explained by varying admixture of recent MI and SA pts in study populations. We conclude that the markedly reduced sens and ppv after recent Q-wave MI are important limitations of the ST/HR slope, but that the method is highly accurate for the identification of 3v CAD in pts with SA, either with or without remote Q-wave MI.

EXERCISE AND RECOVERY SYSTOLIC BLOOD PRESSURES AND PROGNOSIS IN ISCHEMIC HEART DISEASE.

Charles N. Leach, MD, FACC and Elizabeth R. Sunderman, New Britain General Hospital, New Britain, CT and Univ. of CT, Farmington CT.

Abnormal systolic blood pressure (SBP) responses to exercise reflect ischemic heart disease (IHD). Few studies have examined the prognostic value of SBP abnormalities, especially those during the recovery phase. We studied 239 consecutive patients for 5 years after a standard-protocol treadmill. By clinical criteria, 42 were normal (group I), 84 had probable IHD (group II), and 113 had definite IHD (group III). 21 MI's and 8 IHD deaths occurred during followup: none in group I; 4 MI's and 2 deaths in group II, and the remainder in group III. Exercise SBP abnormalities (EAb) were defined as (A) SBP increase $<$ 8mm Hg in any stage; (B) SBP decrease $\geq$ 11mm Hg in any stage; (C) SBP decrease $\geq$ 20 mm Hg in the last exercise minute. Recovery SBP abnormalities (RAb) were: (D) any recovery SBP $\geq$ 10 mm Hg above peak exercise SBP and (E) any recovery SBP $\geq$ 11 mm Hg above the preceding SBP. There was no significant difference in frequency of each EAb among groups I II & III, while RAb (D&E) differences were highly significant ($p < 0.005$ for each). Of all EAb and RAb, only (A) was significantly associated with subsequent MI ($p < 0.025$). 7 of 8 deaths had EAb or RAb. We conclude that SBP response to exercise is a means for identifying pts with IHD and is a predictor of MI. RAb are more sensitive and specific for IHD than are EAb, while EAb have slightly greater prognostic value.

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CORONARY ARTERY DOMINANCE AND MYOCARDIAL MASS REDUCTION AS DETERMINANTS OF TREADMILL STRESS TEST NEGATIVITY IN CORONARY ARTERY DISEASE

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A false negative response during maximal treadmill stress testing (TST) has been a persistent clinical problem in evaluation of coronary artery disease (CAD). This study examines the underlying anatomic causes for this negative electrophysiological response. One hundred fifty false negative TST responders (Grp A) and 150 arteriographically matched positive TST responders (Grp B) are compared. All patients (pts) presented with angina pectoris and 94% experienced angina during TST. No pt had a myocardial infarction within 8 weeks of the TST. LV aneurysm and congestive heart failure pts were excluded. All pts had angiographic evidence of $\geq$ 50% transluminal narrowing of one or more coronary arteries. Coronary system dominance/balance and % wall length motion abnormalities were determined. In Grp A pts, all single vessel CAD lesions occurred in a non-dominant vessel (57) or a dominant vessel with an infarcted LV wall $>$40% of its linear length. Positive pre-infarction TST's were present in 85% of the latter group. Two and 3 vessel CAD pts had multiple non-dominant vessel obstruction (62) while 27 were associated with infarction of a dominant coronary artery. All members of the infarcted group previously had positive TST's. The remaining 4 pts had multi-vessel balanced obstructions. Grp B pts had obstruction of a dominant single vessel (42); dominant single plus additional vessel(s) (79); balanced dominance (13) or 1 or 2 vessel non-dominant obstruction with a diminutive 3rd vessel (6). Infarct size associated with a dominant vessel was always $<$40% of linear wall length. In conclusion, TST negative responders have non-dominant vessel obstruction or significant infarction reduction of active myocardium in a previously dominant perfusion vessel zone.

Wednesday, March 12, 1986
2:00PM-3:30PM, Room #364/365
New Issues in Cardiac Pacing

COMPARATIVE SURVIVAL FOLLOWING PERMANENT VENTRICULAR AND DUAL CHAMBER PACING FOR HIGH DEGREE AV BLOCK IN PATIENTS WITH AND WITHOUT PRE-EXISTENT CONGESTIVE HEART FAILURE.

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To determine whether survival following permanent ventricular pacing differs from survival following permanent dual chamber pacing in patients with chronic high degree atrioventricular (AV) block (Mobitz type II or trifascicular block) we followed 132 patients (Group 1) who received a VVI pacemaker and 48 patients (Group 2) who received a DVI or DDD pacemaker for 1-5 years. There was no significant difference in the mean age, sex, or the incidence of coronary artery disease, hypertension, valvular heart disease, or other chronic co-existent diseases between Groups 1 and 2. Overall, predicted cumulative survival rates at 1, 3 and 5 years were 89%, 76% and 63% respectively in Group 1 and 95%, 82% and 72% respectively in Group 2 (no significant difference). Predicted cumulative survival rates at 1, 3 and 5 years for patients with pre-existent congestive heart failure (CHF) were 85%, 66% and 47% respectively in Group 1 (n=53) and 94%, 74% and 69% respectively in Group 2 (n=20, $p < 0.05$). There was no significant difference in predicted cumulative survival rates between Groups 1 and 2 for patients without pre-existent CHF. The results suggest that permanent dual chamber pacing enhances survival to a greater extent than permanent ventricular pacing in patients with high degree AV block and pre-existent CHF.

SYMPTOM-LIMITED THALLIUM-201 EXERCISE TESTING AT 3 MONTHS AFTER MYOCARDIAL INFARCTION: A COMPARISON WITH SUBMAXIMAL PREDISCHARGE TESTING. **William W. Wilson MD, George A. Beller MD, FACC, Denny D. Watson PhD, Sharon L. Sayre RN, BSN, Donald L. Kaiser PhD, Thomas W. Nygaard MD, FACC, Robert S. Gibson MD. Univ. of VA, Charlottesville, VA**

We prospectively studied 241 consecutive pts with MBCK-confirmed acute MI with predischarge angiography and submaximal exercise Tl-201 scintigraphy (Tl-GXT). Of these, 180 pts returned for symptom-limited Tl-GXT 3 mos after MI. Age was 51±9 yrs; LVEF 50±11%; 33% had non-Q wave MI and 52% had multivessel disease by angiography. At the 3-mo Tl-GXT (Bruce protocol), peak HR ↑ by a mean of 15±22 bpm, peak SBP ↑ by a mean of 15±26 mmHg, and workload ↑ by a mean of 3.3±2.8 METs compared to predischarge Tl-GTX (Naughton protocol). Despite this increase in exercise performance, 94% of pts had either no change (66%) or a decrease (28%) in the number of vascular supply regions considered to be hypoperfused. In only 6% of pts was an additional abnormal region detected. Also, 75% of pts had either no change (48%) or a decrease (27%) in the number of scan segments with Tl redistribution (Rd) despite a higher workload and double product. Infarct zone persistent Tl defects remained constant (39%) or decreased (24%) in number in 63% of pts. Of 148 pts without angina on predischarge Tl-GXT, 22 (15%) developed angina during the 3-mo Tl-GXT. Of 128 pts with no predischarge ST↓, 34 (27%) had ST↓ on the 3-mo test. Finally, of 77 pts with no predischarge Tl-Rd, 21(27%) showed Rd at 3 mos.

Thus, in comparison to submaximal predischarge Tl-GXT, 3-mo symptom-limited testing is associated with little enhancement in the detection of hypoperfused myocardium despite a greater workload. In some pts, Rd actually decreased, possibly due to an interim increase in collateral flow; yet 21 of our 180 pts did develop new Rd at the higher 3-mo workload.

PACEMAKER PROBLEMS AND ASSESSMENT OF MEDICARE GUIDELINES

Lawrence E. Vallario, M.D.,Robert B. Leman,M.D.,FACC, Paul C. Gillette,M.D., FACC, Med. Univ. of S.C., Charleston

The time of occurrence of cardiac pacemaker problems post implantation was identified to assess the adequacy of published federal guidelines for clinic (C) and transtelephonic (TT) followup for single and dual chamber devices. 189 total pacemaker patients (Pts) were followed between July, 1982 and August, 1985. Retrospective examination of these Pts charts was performed to identify pacemaker problems: nonsense, noncapture, battery failure, myoinhibition, muscle stimulation, inadequate safety threshold margin. 32 Pts (17%) were identified as having pacemaker problems. A total of 43 problems were identified which 30 (70%) were corrected by reprogramming and 13 (30%) were corrected surgically (5 Pts due to battery failure). 67% of the problems were found on or during C visit and 33% during TT transmission.

	% of Problems Identified For:	
Time Period	Single Chamber	Dual Chamber
To Problem 0-.5	18%	35%
(Yrs) .5-1	14%	30%
1-4	41%	30%
$>$4	27%	5%

Problems in dual devices occurred more frequently during the first year (65%) vs single devices (32%). During years 1-4 when few problems are expected, 41% of the single chamber problems and 30% of the dual chamber problems occurred. This is a period of time that Medicare guidelines allow for 1 C visit per year for single and 2 visits per year for dual devices. these data suggest: Many pacemaker problems will be missed with TT alone. The majority of problems involving dual devices occurred in the first year. For both dual and single devices an unexpected significant percentage of problems occurred in 1-4 years. Medicare guidelines for year 1-4 may be inadequate for followup.

PACEMAKER DYSFUNCTION OCCURS COMMONLY IN ASYMPTOMATIC PATIENTS.

Peter T. Klementowicz, M.D. and Seymour Furman, M.D., F.A.C.C., Montefiore Medical Center, Bronx, New York

Transtelephonic monitoring and pacemaker clinic checks are accepted methods of pacemaker evaluation. With the increasing complexity of pacemakers, these techniques often do not detect abnormalities of sensing and pacing. We have found that ambulatory monitoring(AM) is a useful adjunct to routine pacer checks and frequently reveals pacemaker malfunction, when it is not otherwise suspected. We evaluated 97 AM in pts with DDD pacemakers and 53 AM in pts with VVI pacemakers. These asymptomatic pts were evaluated in the early post-op period, 2.4 ± 1.8 d post-op for those with DDD and 2.1 ± 1.7 d for those with VVI, and after the 1 mo post-op pacer check, 34.4 ± 7.6 d for DDD and 37.3 ± 12.5 d for VVI. The number of pts with atrial and ventricular sensing abnormalities(SA), non-capture(NC) and myopotential interference(MPI) recorded by AM, are:

			ATRIAL		VENTRICULAR		
PACER	TIME	#PTS	SA	NC	SA	NC	MPI
DDD	Early	69	32	1	2	2	6
DDD	Late	28	7	-	3	1	7
VVI	Early	36	-	-	7	1	-
VVI	Late	17	-	-	7	1	-

Conclusions: The incidence of transient pacer malfunction detected by AM is high. Atrial sensing abnormalities occur in 46% of pts in the early post-op period and decrease to 25% in the late post-op period ($p<.005, \chi^2$). Atrial and ventricular non-capture are rare. Inappropriate ventricular sensing occurs more commonly in VVI pacers, in both the early and late post-op periods ($p<.05, \chi^2$). Myopotential interference occurs in 8.7% of DDD pts in the early post-op period and increases to 25% in the late post-op period.

ELECTRODE MATURATION IN VVI PACEMAKERS AS CONTROLLED BY INTRACARDIAC ELECTROGRAM.

Ulrich J.Winter,M.D., Dieter W.Behrenbeck,M.D., Martin Hoeher,M.D., Johannes Missler, Ursula Dick, Thomas Brill, Vinzenz Hombach,M.D., Hans H.Hilger,M.D., Medical Clinic III, Cardiology, University of Cologne, FRG

The electrode maturation process was controlled in 16 patients (6female, 10 male, aged 60.6± 18.5 ys) whose symptomatic bradyarrhythmias were treated with the Medtronic Spectrax SXT 8423 (VVI) and a traumatic (Biotronik DY, n=10) or a non-traumatic (Vitatron Helifix, n=6) ventricular lead. The telemetry of the intracardiac electrogram (ICEG) was performed at the 1st, 2nd, 5th, 10th, 30th, 60th and 154th± 31 day after implantation (a.i.), taking into account the same conditions (posture, respiration, filters) that modify the ICEG. In all ICEG's but one there was a mean ST-elevation (STE) in the acute phase ranging from 0.45 to 5.50 mV. Two main groups with different STE behaviour were found: one group (n=5, all DY-electrodes) displayed a high ST-amplitude (4.81 ±0.49mV) that decreased to half of its value (2.38± 1.26 mV) within the first 60 minutes a.i.. The other group of acute ICEG's showed a much less pronounced ST-elevation (1.73± 0.84mV) that diminished not before the end of the first month a.i. to it's half. The recovery of the initially reduced R-wave amplitude developed as fast as the STE was pronounced: small R-waves with high amplitude STE regenerated within the first day a.i., small R-waves associated with low STE needed a month to reach an acceptable value. The effects of posture and respiration on the amplitudes of the ICEG decreased as the electrode got fixed by a fibrotic sheet. There was no statistical significant difference between the ICEG's of traumatic and non-traumatic electrodes. Although being a time-consuming method the telemetry of the ICEG enables a reliable control of the maturation process of traumatic or non-traumatic leads.

CAN PACEMAKER IMPLANTATION BE DONE AS AN OUTPATIENT PROCEDURE?

David L. Hayes, M.D., F.A.C.C., Ronald E. Vlietstra, M.D., F.A.C.C., Jane Trusty, R.N., Peter Downing, M.D., Nicholas Cavarocchi, M.D., Mayo Clinic, Rochester, MN.

To determine the feasibility of outpatient pacemaker implantation or of an abbreviated hospital stay following pacemaker implant, we analyzed the hospital course of 100 consecutive patients undergoing pacemaker implant at Mayo Clinic. The patient population included 62 males and 38 females with an average age of 66 years. Single chamber devices were implanted in 51 patients and dual chamber devices in 49 patients. Average acute thresholds were: atrial 0.96 V, 2.2 mA, 2.9 mV P wave; ventricular 0.5 V, 1.0 mA, 9.5 mV R wave. All patients were followed at least 72 hours in the hospital. Pneumothorax requiring chest tube placement occurred in 2 patients. Ventricular lead dislodgement occurred in 2 patients, 1 pacemaker dependent and 1 not. Atrial lead repositioning was required in 1 patient. Cardiac tamponade occurred in 1 and required echo-directed pericardial tap. Reprogramming of atrial sensitivity was necessary in 5 patients to correct atrial undersensing; ventricular oversensing was corrected with reprogramming in 1 patient; and extension of the atrial refractory period to prevent pacemaker-mediated tachycardia was needed in 3 patients. The 6 complications requiring an invasive procedure were all clinically evident within 24 hours post-implant. While the need for reprogramming was recognized at up to 24 hours there were no further new events occurring in the 24 to 72 hour period. Based on this data we do not advocate pacemaker implantation as an outpatient procedure but recognize that patients could be discharged from the hospital 24 to 48 hours following the procedure with low likelihood of further new events.

SHOULD THE AUTOMATIC IMPLANTABLE DEFIBRILLATOR PACE?

Peter D. Chapman, M.D., Sharon E. Duquette, R.N., Jule N. Wetherbee, M.D., Paul J. Troup, M.D., F.A.C.C., Medical College of Wisconsin, Milwaukee, Wi.

To assess the need for pacing in patients (pts) with implanted defibrillators (IDs), we examined the length of post-shock pauses (PSPs) during intraoperative defibrillation threshold (DFT) testing in 17 pts undergoing ID generator placement with (9 pts) or without (8 pts) concomitant lead placement. Pts with pacemakers and those requiring additional cardiac surgery or cardiopulmonary bypass were excluded. Two epicardial patch electrodes were employed for defibrillation in all pts. DFT testing was performed with truncated exponential pulses from an external cardioverter defibrillator. Twenty joules (J) was tested initially, and if successful in terminating ventricular fibrillation, testing continued with energy output decrements of 5 J until DFT was defined. The ID generator was then tested. The PSP was measured as the time from termination of the arrhythmia to the first non-ventricular tachycardia/fibrillation complex. The mean pause during the generator trials (25 to 30 J discharges) was 918.2 msec (range 400 to 1,780). There was no significant difference between the generator alone versus generator plus lead implant groups (963.8 ± 411.4 versus 877.8 ± 350.8; mean ± S.D.) and no significant difference between the mean length of the PSP at 10, 15, or 20 J during DFT testing (1,061.7 ± 594.4, 934.3 ± 386.0, and 1,004.3 ± 534.3 respectively). We conclude: 1) over the range of energies tested, the PSP is not related to shock energy, 2) prolonged PSPs do not occur following ID discharges through two ventricular patch electrodes, and 3) "back-up" post-shock pacing appears unnecessary.

Wednesday, March 12, 1986
4:00PM–5:00PM, Room #364/365
Devices for Arrhythmia Therapy: The Implantable Defibrillator

MORBIDITY, MORTALITY AND DEVICE FAILURE ASSOCIATED WITH THE INTERNAL AUTOMATIC CARDIOVERTER/DEFIBRILLATOR
Francis E. Marchlinski, MD, FACC, Belinda Flores, MSN, University of Pennsylvania, Philadelphia, PA

The automatic internal cardioverter defibrillator (AICD) has been reported to improve survival with low risk. The AICD generator and leads were implanted in 26 patients (pts) with refractory ventricular tachycardia/fibrillation (VT/VF), and a patch lead was placed at cardiac surgery in seven other pts. During 11±6 mos, the AICD discharged in nine pts (35%) for documented (7 pts) or suspected (2 pts) sustained VT/VF. No sudden deaths occurred. There were 31 complications in 17 pts. The patch lead or AICD implant may have contributed to early postoperative death with coronary artery erosion beneath patch in one pt and refractory heart failure in a second pt. Other major complications included subclavian vein thrombosis, postoperative stroke after conversion of atrial fibrillation by AICD, and thoracotomy site infection in one pt each. The AICD discharged when pt was asymptomatic with rhythm unknown in 4 pts, sinus in 3 pts, nonsustained VT in 2 pts, and atrial fibrillation in one pt. Other complications included lead migration (3 pts), atelectasis/pneumonia (4 pts), symptomatic pleural effusion (3 pts), seroma at AICD site (3 pts), pneumothorax (2 pts), and subcutaneous hematoma (one pt). In addition to complications, 4 pts had early generator failure, 3 pts had VT with rates too slow to trigger the AICD during chronic amiodarone therapy, and 3 pts (2 on amiodarone) had VF which could not be terminated by AICD during postoperative testing despite successful interoperative testing. One other pt had delayed sensing of VF due to interference from unipolar RV pacing. Thus, although the AICD can be life saving, significant morbidity and potential mortality may accompany its use. Potential complications and drug/pacing interactions with the AICD should be considered at time of pt selection.

COMPLICATIONS WITH THE AUTOMATIC IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR.
Edward V. Platia, MD, FACC, Lawrence S.C. Griffith, MD, FACC, Philip R. Reid, MD, FACC, Thomas Guarnieri, MD, FACC, Levi Watkins, Jr., MD, Morton M. Mower, MD, FACC, M. Mirowski, MD, FACC, The Johns Hopkins Medical Institutions and Sinai Hospital, Baltimore, MD; and Washington Hospital Center, Washington, DC.

We reviewed the complications encountered in 116 patients (pts) with the automatic implantable cardioverter-defibrillator (AICD). Our population consisted of 86 men and 30 women, mean age 55 yr (range 19-76 yr), with sustained VT or VF in whom we implanted the 2nd generation AICD. Over the period of study, 146 pulse generators were implanted in 116 pts. Followup averaged 15 mo, (range 4-48 mo), during which time there were 21 deaths, of which 3 were sudden. 109/116 pts had an active AICD at hospital discharge and 25 complications, none lethal, occurred in 23 pts. Post-operative infection of the pulse generator pocket occurred in 7 pts, all of whom had the generator (or a pulse generator simulator box) implanted. In 2 of these pts infection tracked to the heart via AICD lead, prompting extirpation and replacement of both pulse generator and leads. SVC lead displacement occurred in 4 of the first 31 implants, but has not occurred following adoption of improved lead fixation at the venous entry site. Six pts experienced inappropriate AICD discharge during supraventricular tachycardias when the ventricular rate was above 150 bpm. Beta-blockers were required to prevent recurrences. Other complications: subclavian vein thrombosis (2), pneumothorax (1), lead fracture (1) and need for psychologic support (2). In conclusion, nonfatal AICD complications are relatively common. Particular attention should be paid to minimize wound infections, lead migration, and unwanted AICD discharges during supraventricular tachycardias.

CAUSES OF DEATH IN PATIENTS WITH THE INTERNAL DEFIBRILLATOR: ANALYSIS OF 188 PATIENTS AT 60 MONTHS FOLLOWUP.
Igor Singer, M.B.,B.S., Philip R. Reid, M.D., F.A.C.C., Lawrence S.C. Griffith, M.D., F.A.C.C., Morton M. Mower, M.D., F.A.C.C., Enrico P. Veltri, M.D., M. Mirowski, M.D., F.A.C.C., Edward V. Platia, M.D., F.A.C.C., Thomas Guarnieri, M.D.,F.A.C.C., Eva Magiros, M.D., Sara Schmitt, B.S., Juan Juanteguy, M.D., Levi Watkins, M.D. The Johns Hopkins and Sinai Hospitals, Baltimore, Maryland

Between Feb, 1980 and Jul,1985, 188 patients were evaluated for the automatic internal cardioverter defibrillator (AICD). There were two groups: LEADS ONLY (N=32) patients who received only the lead system with (88%)/without additional cardiovascular (CV) surgery in anticipation of a pulse generator. AICD patients (N=156) who received the leads and pulse generator with (14%)/ without additional CV surgery. The groups were not different with respect to the type of heart disease (80% coronary disease;20%2 cardiomyopathy), sex, or ejection fraction (33 vs 31%).

In LEADS ONLY patients 17 deaths occurred (53%) over 39 days (mean): 8/32 (25%) from arrhythmias; 4/32 (13%) from heart failure with/without acute infarction; 5/32 (16%) from post-operative complications. In-hospital death from ventricular tachycardia/fibrillation (VT/VF) occurred in 6/32 (19%).

In AICD patients 35 deaths (22%) occurred over 367 (mean)days: 17/156 (11%) from arrhythmias; 13/156 (8%) from heart failure with/without infarction; 5/156 (3%) from post-operative complications. In-hospital death due to VT/VF occurred in 2/156 (1%).

These results demonstrate:1) The LEADS ONLY group has higher mortality than the AICD group over shorter followup (39 vs 365 days).;2) LEADS ONLY patients died more frequently from arrhythmias (p=.04); 3) in-hospital death due to VT/VF is significantly greater in the LEADS ONLY patients (19% vs 1%,p<.007); and 4) suggest that the AICD significantly reduces sudden death in patients at high risk of VT/VF.

IACD - PATIENT AND BATTERY LONGEVITY AND SHOCK DELIVERY
Mark D. Gabry, M.D., Richard Brodman, M.D., Debra Johnston, R.N., Rosemary Frame, R.N., John D. Fisher, M.D., F.A.C.C., Seymour Furman, M.D., F.A.C.C. Montefiore Medical Center, Bronx, New York

Between 5/82-8/15/85, 20 pts (14 M and 6 F-average age 57.8) 38-76) out of approximately 250 who were evaluated by PES for sustained ventricular tachycardia and/or fibrillation (VT/VF) underwent initial implantation of an implantable cardioverter defibrillator (IACD). Eighteen had coronary artery disease (CAD), 2 non-ischemic cardiomyopathy (1 with mitral valve prolapse - MVP) and 1 CAD and rheumatic heart disease. The avg ejection fraction (EF) was 28% (9-64%) and all remained with VT/VF after multiple drug trials including 3 with endocardial resection. One (1/20) 58 yr old F with MVP and an initial EF of 64% died 5 mos postimplant of a nonarrhythmic cardiac event after MV replacement and intraoperative AV node ablation. She had received 47 shocks for VT/VF and recurrent atrial fibrillation (AF).Although 55% (11/20) never had a spontaneous shock for VT/VF and all are alive, 45% (9/20) experienced 1 or more, the 1st event occurring within 5 mos in 7 of 9. If the 1st shock prevented death, the cumulative survival rate at 30 mos would have been 54% rather than 95%. Eleven (11/20) pts experienced spontaneous shocks: 9 (9/11) appropriate, 2 (2/11) inappropriate, but at least 4/9 received both appropriate and inappropriate shocks (sinus tachycardia, AF and/or pacemaker related). Fourteen have been explanted: 9-battery depletion (BD); 1-no output failure; 2-infection and 1-lack of sensing and insufficient output;1-sensing problems. The number of shocks given does not influence IACD longevity unless extensively used. The 9 depleted units lasted 17 mos (11-22). The shortest (11 mos) discharged 30%, the longest (22 mos) 18%, the others 12% or less. The 4 (4/9) units that never gave spontaneous shocks averaged 17.5 mos (15-19) while the 5 (5/9) that did, averaged 17 mos (11-22). Elimination of the glass corrosion battery failure mode in Jan 1984 has not prevented early achievement of the Elective Replacement Indicator (ERI) (approx. 90% BD & 3.3 mos monitoring time). 83% (5/6) with greater than 6 mos follow-up time have reached this ERI within 8 mos (5-8 mos). The validity of the ERI is uncertain as none have failed and 3 remain active 10-11 mos later.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #157
Congenital Heart Surgery

DOES THE SUBCLAVIAN FLAP OPERATION DECREASE THE NEED FOR REOPERATION FOLLOWING COARCTATION REPAIR IN INFANCY?

R.H. Beekman, MD, FACC, A.P. Rocchini, MD, D. Behrendt, MD, FACC, E.L. Bove, MD, FACC, A. Rosenthal, MD, FACC. C.S. Mott Children's Hospital, Ann Arbor, MI.

To assess the influence of surgical technique on the need for reoperation (reop) after coarctation (coa) repair in infancy, data were compared for 55 consecutive survivors of left subclavian angioplasty (LSA) (1977-85) and 44 consecutive survivors of end-to-end repair (END) (1960-1977). Mean age at operation for LSA was 1.5±0.3 months (±SEM; range 0.1-12) and for END was 2.7±0.4 months (range 0.1-11) ($p<.05$). There was equal distribution of complex anatomy and arch hypoplasia between groups. Follow-up was 2.6±0.3 yr for LSA and 8.0±0.8 yr for END ($p<.01$). Indication for reop was resting coa gradient >40mmHg and upper extremity hypertension. Reop was performed during the first 3 postop years in 5 LSA and 3 END pts, and by the 7th postop year in a total of 5 LSA and 8 END pts. The 3 and 7 year reop rate (per 100 pt-years) and individual reop risk (%; incidence density method) for each surgery are given below. NS = not significant.

	LSA		END		P VALUE	
REOP	3 YR	7 YR	3 YR	7 YR	3 YR	7 YR
RATE	4.1	3.1	2.4	3.1	NS	NS
RISK	12	20	07	20	NS	NS

Compared to END, the relative risk for reop after LSA was 1.7 at 3 yr (95% CI: 0.8, 3.5) and 1.0 at 7 yr (95% CI: 0.99, 1.01). The risk of requiring reop during the first 7 postop years was 20% regardless of the type of initial surgery. Thus, LSA does not decrease the need for reop following coa repair in infancy.

REGIONAL AND GLOBAL LEFT VENTRICULAR FUNCTION IN ANOMALOUS ORIGIN OF LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK.

Azaria J.J.T. Rein, MD, Steven D. Colan, MD, Ira Parness, MD, Stephen P. Sanders, MD, Department of Cardiology, The Children's Hospital, Boston, MA.

Five infants (2-8.5 months old) had serial 2D echo evaluation before and 6-36 months after intrapulmonary artery baffle repair of anomalous left coronary artery (ALCA) and were compared with 17 infants (10 normal and 7 with idiopathic dilated cardiomyopathy) matched for age. Quantitative analysis of regional wall motion (center of mass model), end-diastolic volume (EDV), EF, LV mass, and the mass to volume ratio (MVR) were calculated using a computerized review center.

	EF %	EDV ml/m^2	Mass ml/m^2	MVR
Normal	66.5±5.9	60±15	64±13	1.03±0.11
Cardiomyopathy	23.0±13	287±144	182±124	0.63±0.11
ALCA-Preop	22.2±11.6	268±97	141±55	0.70±0.14
ALCA-Postop	59.0±8.1	85±14	90±15	1.06±0.14

Severe hypokinesis of all LV segments was noted in the patients with ALCA without significant regional variation in wall motion, a pattern indistinguishable from that seen in the cardiomyopathy group. The EDV and mass were markedly enlarged and the EF depressed in the patients with ALCA, as in those with cardiomyopathy. After repair of ALCA, the EF rose to near normal while the EDV and mass decreased. The MVR, which had been low pre-operatively, became normal after surgery.

We conclude that: 1) infants with ALCA generally exhibit global LV hypokinesis indistinguishable from cardiomyopathy rather than specific segmental abnormalities, 2) as in cardiomyopathy, preoperative LV dysfunction in ALCA is associated with inadequate hypertrophy leading to an abnormally low MVR, 3) following successful surgery of this type for ALCA, there is a rapid reduction in LV volume along with regression of hypertrophy with dramatic recovery of systolic function.

FONTAN PROCEDURE FOR CHILDREN LESS THAN FIVE YEARS OF AGE

W. James Parks, M.D.: Kenneth J. Dooley, M.D.,FAAP; Willis Williams, M.D.; Pediatric Cardiology, Emory University School of Medicine

Sixteen (16) patients underwent Fontan procedure for treatment of tricuspid atresia complex (12), single ventricle, left atrioventricular valve atresia (1), pulmonary atresia (2), and hypoplastic left ventricle with ventricular septal defect (1) between October, 1981 and July, 1985. All patients underwent a pallative procedure before Fontan. Fifteen (15) patients survived surgery and eleven (11) were alive at discharge (69% survival). All patients over two years of age (8/8) survived (100%). Three of eight patients, under 2 years of age survived (37.5%). Pulmonary artery pressure (PAP) was measured directly or via pulmonary vein wedge in 14 patients and was used to calculate pulmonary resistance (PR). Left ventricular end diastolic pressure (LVed) was less than 12 mmHg for the group with a mean of 7.6 mmHg.

	PAP (range)	PR (range)	LVed (range)
<2yrs (6)	16.2(6-27)	1.70(0.5-2.5)	7.5(4-11)
>2yrs (8)	12.3(9-15)	1.54(0.8-3)	7.75(3-12)
Deaths (3)	20.3(14-27)	2.23(2.1-2.3)	8.6(7-11)

Pulmonary artery cross sectional area/indexed, cardiac output, pulmonary to systemic flow ratio, pulmonary artery to aortic ratio, aortic cross clamp time, pump time, and arrest time were all evaluated. No single factor other than age influenced the outcome. Although numbers are small a pulmonary vascular resistance of greater than two units may influence the outcome.

VENTRICULAR FUNCTION IN PATIENTS WITH OBSTRUCTED RIGHT VENTRICULAR-PULMONARY ARTERY CONDUITS.

Imre Palik, MD, Thomas P. Graham, MD, FAAC, Judith Burger, RN. Vanderbilt University, Nashville, TN 37232.

Children with right ventricular (RV) to pulmonary artery (PA) conduits frequently have progressive RV pressure overload. The effect of the increased RV pressure on ventricular function and the optimal timing for reoperation in order to prevent irreversible ventricular dysfunction are unclear. Accordingly RV and left ventricular (LV) end-diastolic volumes (EDV) and ejection fractions (EF) were assessed using biplane cine angiography and radionuclide angiography (RNA) in 18 patients studied an average of 5.2 yr after valved conduit repair for RV-PA discontinuity. There were 7 repairs done in infancy (group I) and 11 done between 2-9 yr of age (group II). Values below are $\bar{x} \pm$ S.D.

GROUP	RVP	RVEF	LVEF	RVEDV	RV-PAP	RVEDP
I	92±21	0.60±0.10	0.68±0.08	116±34%	64±24	8±2
II	128±53	0.43±0.11*	0.56±0.10*	119±29%	84±66	13±7

*$p<0.05$ vs. Group I. P = pressure in mmHg

There was an inverse relationship between RVEF and age at repair. $r=0.714$, $p<0.005$. In addition, the RNA RVEF response to exercise was abnormal in 7/7 and the LVEF abnormal in 7/8 with all but one of these patients operated upon after 2 yr of age. Abnormal pump function is prevalent in patients with obstructed RV-PA conduits whose initial repair is performed after infancy whereas patients with repair during infancy show normal function despite similar RV pressure overload. The progressive decrease in RVEF with age indicates the inadequacy of hypertrophy and other compensatory mechanisms to normalize RV pump function in older children with obstructed conduits. Further prospective data are needed to discern risk factors for permanent RV dysfunction in this clinical setting.

CRYOABLATIVE TECHNIQUES IN THE TREATMENT OF CARDIAC TACHYARRHYTHMIAS

David A. Ott, M.D., F.A.C.C., Arthur Garson, M.D., F.A.C.C. Denton A. Cooley, M.D., F.A.C.C., Richard T. Smith, M.D. and Jeffrey Moak, M.D. Texas Heart Institute, Houston, TX

Forty-four patients underwent electrophysiologic mapping and definitive surgical treatment for potentially lethal and refractory cardiac tachyarrhythmias using cryoablative (cryo) techniques. Included were 16 patients with supraventricular tachycardia due to accessory pathways (Kent bundle) in the anterior or posterior paraseptal location. Cryo was successful in abolishing tachycardia in 93.7% (11/12). Seventeen of 18 patients with atrial ectopic tachycardia were treated by cryo alone or in combination with excision of the atrial appendage with success in 13 (76.5%). Five of these were left atrial foci cured by cryo alone. Thirteen right atrial foci were treated by excision of the appendage only (1), excision of the appendage and local cryo (8), and cryo alone (4). Five right sided lesions required cardiopulmonary bypass and 2 of these underwent partial atrial disconnection after excisional and cryo techniques failed to control the tachycardia. Multiple ectopic atrial foci were common (8) and successful cryo was accomplished in 100% of patients with a single atrial ectopic focus (9), but in only 50% of these with multiple foci. Seven of 13 infants with critical ventricular tachycardia were treated by cryo at the site of the ectopic focus either alone or in combination with excision of the area (5). Elimination of tachycardia was accomplished in all 7 patients. One patient with ventricular tachycardia after repair of tetralogy of Fallot underwent successful cryo of an ectopic focus on the crista supraventricularis. We conclude that cryo techniques are effective and safe in selected cases of tachycardia and may be used alone or in combination with other methods to effect a high rate of cure.

LONG-TERM FOLLOW-UP AFTER SURGICAL CORRECTION OF WOLFF-PARKINSON-WHITE SYNDROME IN 45 PATIENTS

Tim A. Fischell, M.D.; Edward B. Stinson, M.D., FACC; Geraldine C. Derby, R.N.; Charles D. Swerdlow, M.D., FACC; Stanford University Medical Center, Stanford, CA.

Surgical correction of Wolff-Parkinson-White syndrome (WPW) was performed in 45 consecutive patients (pts), age 2-59 yrs. Preoperatively, 40 pts had reciprocating tachycardia refractory to 2.9+1.8 antiarrhythmic drugs, and 13 had atrial fibrillation (shortest RR interval = 212+51 ms). Intraoperative mapping identified 48 accessory pathways: 33 left free wall, 8 posteroseptal, 5 right free wall, and 2 anteroseptal. The principal operative procedure was endocardial incision in 43 pts, endocardial cryoablation in 1 pt, and epicardial cryoablation without dissection of the atrioventricular fat pad in 1 pt. Adjunctive procedures were coronary bypass grafting in 2 pts and mitral valve replacement in 2 pts. Three pts had perioperative complications: 1 pt had a perioperative stroke with subsequent resolution of the neurologic deficit; 2 pts with posteroseptal accessory pathways had asymptomatic complete heart block which resolved within 2 wks. No pt had atrial fibrillation postoperatively. At postoperative electrophysiologic study, the pt who underwent epicardial cryoablation had inducible reciprocating tachycardia; no other pt had accessory pathway conduction. Two pts with normal postoperative electrophysiologic studies had intermittent delta waves on postoperative ECGs, similar to preoperative delta waves in 1 pt and different in the other. During a mean follow-up of 2.1 yrs (range 1 mo - 5.9 yrs), 1 pt with Ebstein's anomaly had supraventricular tachycardia of uncertain mechanism, 1 pt had late recurrence of delta waves without arrhythmias, and 3 pts had palpitations due to extrasystoles. All 12 pts whose arrhythmias limited employment preoperatively have returned to work. By actuarial analysis at 1, 2, and 3 yrs, 98%, 94%, and 94% of pts were free of arrhythmias; all are alive.

Conclusions: Surgical correction of WPW provides excellent long-term arrhythmia control with low morbidity. Pts whose arrhythmias limited employment preoperatively return to work. Delta waves may persist or recur without return of arrhythmias. Postoperative palpitations may not correlate with tachyarrhythmias.

Wednesday, March 12, 1986
4:00PM-5:00PM, Room #157
Studies of Myocardial Metabolism by PET and NMR

RELATION BETWEEN BLOOD FLOW AND GLUCOSE METABOLISM IN HYPOPERFUSED VENTRICULAR SEGMENTS IN CHRONIC ISCHEMIC HEART DISEASE.

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Residual glucose metabolism distinguishes hypoperfused, ischemic tissue from regions of infarction. To assess the relation between flow reduction and metabolic activity, PET with tracers of flow (N-13 ammonia, NH_3) and glucose metabolism (F-18 deoxyglucose, FDG) was performed in 13 patients with chronic ischemic heart disease. Septal, anterior, lateral, apical and inferior segments were analyzed. Tracer concentrations were normalized to peak activity over the entire heart and calculated for each of the 12, 30° sectors in the circumferential profile of each cross-sectional plane. Ratios derived from normals were used to correct relative tissue concentrations for partial volume effect. Using previously published criteria, 34 segments with depressed NH_3 activity were identified. In 20 segments with concurrently reduced FDG activity (PET infarct), mean relative NH_3 activity was 44.7±10.8%, while in 14 segments with preserved FDG activity (PET ischemia), mean NH_3 activity was 61.2±20.0% ($p<0.01$). Although the decrease in FDG activity paralleled that of NH_3 in PET infarction (44.0±9.1%, $FDG/NH_3=0.99$), FDG uptake was augmented relative to flow in segments of PET ischemia (83.8 ± 10.7%, $FDG/NH_3=1.37$). Thus, moderately severe reductions in perfusion are associated with residual metabolic activity and accelerated glucose utilization relative to blood flow. More severe reductions in flow are associated with concordant decreases in glucose utilization, suggesting irreversible tissue necrosis.

RELATIVE REDUCTION OF EXOGENOUS GLUCOSE UTILIZATION IN THE SEPTUM OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY.

Maleah Grover-McKay, M.D. F.A.C.C., Markus Schwaiger, M.D., Janine Krivokapich, M.D., F.A.C.C, Michael E. Phelps, Ph.D., Heinrich R. Schelbert, M.D., F.A.C.C., UCLA School of Medicine, Los Angeles, California.

We examined regional myocardial glucose utilization with F-18 deoxyglucose (FDG) and positron emission tomography (PET) in 10 patients (pts) with hypertrophic cardiomyopathy (HCM). Six pts were studied at rest (R), 3 pts during maximal exercise (EX), and 1 pt at both R and EX (11 studies). On visual analysis, FDG uptake in the septum (S) was markedly reduced relative to the lateral wall (LW) in 6 studies and only mildly reduced in 5 studies. Echocardiographic (echo) wall thickness was used to correct underestimation of regional FDG uptake by PET (partial volume effect). The S/LW ratio for wall thickness averaged 1.9 ± 0.3; i.e., S was 90% thicker than LW. In contrast, corrected FDG concentrations were reduced in S relative to LW. This decrease was less in pts with visually mild (37.0 ± 6.2%) than in pts with visually marked FDG reduction (54.8 ± 9.8%; $p<.01$). Marked septal FDG reduction was always present during EX (4/4), but only in 2/6 at R, and was present during EX but not R in the pt with both R and EX. Echo HCM severity, on a scale of 10 (based on thickness of S, extent of S hypertrophy, and extension of hypertrophy to the anterolateral wall), was similar between pts with mildly and markedly reduced septal FDG (7.5 ± 1.3 vs 5.6 ± 2.2). We conclude that in HCM pts exogenous glucose utilization is relatively reduced in the hypertrophied septum compared to the lateral wall. The underlying pathophysiology remains uncertain and warrants further investigation.

INFLUENCE OF WORK ON MYOCARDIAL pH DURING ACIDOSIS.

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We sought to assess the effects of acidosis on ventricular function and the biochemical milieu during varying calcium concentrations $[Ca]_o$ and working conditions. To this end, we measured intracellular pH $[pH]_i$ and high energy phosphates (ATP,PCr) by nuclear magnetic resonance spectroscopy. Coronary flow, developed pressure (Dev P), and maximum dP/dt were also measured during 30 min. of induced acidosis and 15 min. re-equilibriation each at varying $[Ca]_o$ and (DevP) in isolated perfused rat hearts.

$[Ca]_o$ (mM)	0.8	2.0	4.0	4.0
Workload			High	Low
Dev P (mmHg)	41±7	112±12	208±55	32±3
	Results Expressed as % of Control			
$[Ph]_i$	6.82±.06	6.90±.03	6.42±.13	6.90±.03
ATP	1.03±.09	1.08±.21	0.68±.16	1.00±.07
PCr	0.94±.13	0.76±.13	0.35±.19	0.86±.08
DevP	0.77±.16	0.77±.04	0.29±.25	0.55±.15
dP/dt	0.86±.26	0.78±.18	0.21±.10	0.65±.18
Flow (n=5)	0.95±.10	0.96±.09	0.51±.17	0.90±.12

Return to control was observed in all preparations except that related to "high workload." Intracellular pH, ventricular function and flow, as well as high energy phosphates, were severely depressed only in the "high workload" model. Induced either by calcium or loading, work was the major determinant of biochemical deterioration and ventricular dysfunction was secondary.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #267
Cardiomyopathy: Prognosis, Arrhythmia

UNEXPECTED POOR SURVIVAL WITH DILATED CARDIOMYOPATHY WHEN TRANSPLANTATION DENIED DUE TO LIMITED SYMPTOMS

L. Warner Stevenson, M.D., Michael B. Fowler, M.D., John S. Schroeder, M.D., F.A.C.C., Rex N. MacAlpin, M.D., F.A.C.C., Kathleen A. Dracup, R.N., Victoria Fond. UCLA and Stanford Medical Centers, Los Angeles and Stanford, California.

When referred for transplantation, patients with dilated cardiomyopathy (CM) may have limited symptoms despite abnormal hemodynamics. To study the natural history of this patient group, outcomes were obtained and compared to clinical and hemodynamic data for 26 consecutively referred patients with non-ischemic dilated CM who were rejected for transplantation due to lack of severe symptoms.

Actuarial survival following evaluation was 42% at 1 yr., and 24% at 2 yrs. When patients dying within 1 yr. were compared to 1 yr. survivors, there were no significant differences in clinical class (2.5 vs 2.5), ejection fraction (16% vs 17%), stroke volume index (27 vs 29 cc/m^2), pulmonary wedge pressure (22 vs 17 mmHg), right atrial pressure (6 vs 4 mmHg), or systolic blood pressure (102 vs 96 mmHg).

9/11 first yr. deaths were sudden. Documented history of ventricular arrhythmias (non-sustained or sustained ventricular tachycardia, ventricular fibrillation, or sudden death) was present at initial evaluation in 8/9 patients who died suddenly, 0/2 patients who died from hemodynamic failure, and 1/10 patients who survived the first yr.

Patients with dilated CM rejected as "too well" for transplantation have an unexpectedly high mortality. Hemodynamics do not identify risk of early death, which is usually sudden. For patients referred with mildly symptomatic CM, ventricular arrhythmias may be an indication for early transplantation.

DEMONSTRATION OF CARDIAC ALLOGRAFT REJECTION IN RATS USING IN VIVO P-31 NMR SPECTROSCOPY

Robert C. Canby, M.E.E., William T. Evanochko, Ph.D., Leslie V. Barrett, B.S., Robert E. Foster, B.S., Russell C. Reeves, M.D., F.A.C.C., and Gerald M. Pohost, M.D., F.A.C.C., University of Alabama at Birmingham.

Monitoring of human cardiac allograft rejection currently requires endomyocardial biopsy. A noninvasive technique to assess the rejection of transplanted organs would greatly simplify the medical management of the transplant patient. In vivo P-31 NMR spectroscopy has been successful in monitoring phosphorous metabolites in both man and animal models. We have applied this technique to noninvasively assess cardiac allograft rejection in a rat model. Brown Norway rat hearts were placed subcutaneously into the anterior region of the neck of Lewis recipients. Control isografts employed Lewis donors and recipients. Transplanted hearts were monitored using surface coil P-31 NMR spectroscopy (4.7 Tesla) daily for eight days. Phosphocreatine to inorganic phosphate ratios (PCr/Pi) were serially determined throughout the course of rejection. To allow recovery from surgical compromise day 2 was used as baseline PCr/Pi. Overall, serial P-31 spectra of isografts showed either no significant change ($p>.05$) or an increase in PCr/Pi ($p<.02$), whereas allografts demonstrated a continual decrease in PCr/Pi. In the allograft group the decrease in PCr/Pi was not statistically significant at day 3 ($p=.25$), but was significant by day 4 ($p<.04$) and at later days ($p<.005$). A comparison between isograft and allograft PCr/Pi showed no significant difference until day 4 ($p<.01$). The difference became greater at subsequent time intervals ($p<.003$). These data suggest that in vivo P-31 NMR spectroscopy may offer a noninvasive method to monitor cardiac allograft rejection.

SPONTANEOUS VARIABILITY OF VENTRICULAR ARRHYTHMIA IN HYPERTROPHIC CARDIOMYOPATHY

John P. Mulrow, MD, Michael JR Healy, MA, William J. McKenna, MD. Royal Postgraduate Medical School, London.

Asymptomatic ventricular arrhythmias are common in hypertrophic cardiomyopathy (HCM) and are associated with sudden death. To assess the variability of premature ventricular complexes (PVC) and the duration of ECG monitoring necessary to exclude VT, 16 pts with HCM who had VT on the first 48 hours of ECG monitoring were studied. They had 48 - 168 hours of ECG monitoring (median 72) off cardiac medication within a one year period. Daily PVC rates were 2 - 17693 (median 172); 108 episodes of VT (0 - 10, mean 1.5 per day) were recorded. Logarithmic transformation and analysis of variance were applied to PVC counts of 10 pts with PVC's during > 18 hours of each 24 hour period. The root mean square difference in PVC frequencies between corresponding 8 hour and 24 hour periods was 48% and 38%. A sine curve fitted to these PVC counts revealed a circadian rhythm with a peak between 23:30 and 02:30 hours in 5 pts and between 12:40 and 17:40 hours in 5 pts. A 73% reduction in mean PVC frequency on corresponding 8 hour or a 61% reduction in consecutive 24 hour periods was necessary to attribute an effect to intervention with 95% confidence. The likelihood of excluding VT on K days of ECG monitoring was determined. The probability of failing to detect VT was 48% for 24 hours of ECG monitoring, 23% for 48 hours and 11% for 72 hours. We conclude: In pts with HCM and VT (1) there is substantial biologic variability for PVC frequency. (2) A circadian rhythm indicates similar hours of monitoring for PVC frequency should be compared to assess an intervention effect. (3) 48 - 72 hour ECG can be used to assess drug therapy for VT while 5-6 days of monitoring is required to exclude VT in all pts with HCM.

PROGNOSTIC SIGNIFICANCE OF MYOFILAMENT LOSS IN PATIENTS WITH IDIOPATHIC CARDIOMYOPATHY DETERMINED BY ELECTRON MICROSCOPY. Elizabeth H. Hammond, M.D., Jeffrey L. Anderson, M.D., F.A.C.C., Ronald L. Menlove, Ph.D., University of Utah, LDS Hospital, Salt Lake City, Utah

Light microscopic (LM) analysis of endomyocardial biopsy samples in idiopathic dilated cardiomyopathy (IDC) has usually been nonspecific, both diagnostically and prognostically. However, electron microscopy (EM) has been inadequately explored. We evaluated biopsies from 63 consecutive patients (pts) with clinical features of IDC by EM and LM. LM findings were nonspecific in 49, and showed cardiac inflammation in 14. Ten EM indices, potentially useful as predictors of disease severity, were assessed, including myofilament loss. Myofilament loss was graded by EM from 0 (none) to 3+ (extensive). EM findings were correlated with pt survival during a subsequent followup interval of 1-48 mo (mean 18.3 mo). Survival was found to signifiicantly correlate with myofilament loss on EM, as shown below (X^2=9.3, p<.026).

Myofilament Loss	Pt Alive	Pt Dead	% Mortality
0	20	1	5%
1+	24	4	14%
2+	17	9	35%
3+	2	2	50%

Mortality in pts with 2-3+ myofilament loss was 37% vs 10% in those with grade 0-1+ loss (p=.05). The sensitivity of the mortality determination was 0.69, specificity 0.69, positive predictive value 0.33, and negative predictive value 0.9. Similar mortality trends were found in subgroups of pts both with and without cardiac inflammation, but were significant only for the latter (larger) subgroup. In conclusion myofilament loss, graded semiquantitatively by EM, appears to be a significant and clinically valuable predictor of mortality risk in pts with IDC.

MALIGNANT VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH IDIOPATHIC CARDIOMYOPATHY
Michael A. Ruder, M.D., Michael Eldar, M.D., Joseph A. Abbott, M.D., F.A.C.C., John J. Seger, M.D., Melvin M. Scheinman, M.D., F.A.C.C., University of California, San Francisco, CA.

We evaluated 22 patients (pts) with idiopathic cardiomyopathy (ICM) and sustained ventricular tachycardia (VT) (14) or ventricular fibrillation (VF) (8). Mean age was 56 ± 14 years, mean ejection fraction was 29 ± 7 and 36% were in NYHA functional class III or IV. Programmed ventricular stimulation (PVS) was performed in 18 of the 22 and replicated the clinical arrhythmia in 17 (94%). These pts underwent serial drug testing with conventional and experimental drugs; those with persistently inducible arrhythmias were treated with amiodarone (A). In 4 pts, empiric drug trials were used because of the almost incessant nature of the tachycardia. Chronic therapy consisted of A alone (18), A and mexiletine (1), quinidine (1), bepridil (1) and lorcainide (1). Over a mean follow-up interval of 17.3 ± 8.0 months, 77% are well, 1 died of CHF, 1 died suddenly (A) and 1 had recurrent VT (lorcainide). Two pts discontinued A and died suddenly. Conclusions: 1) In pts with malignant ventricular arrhythmias and ICM, PVS is extremely sensitive in replicating the clinical arrhythmia. 2) Conventional antiarrhythmic therapy is seldom effective in preventing VT inducibility. 3) A appears to be highly effective in prevention of VT recurrence or sudden death.

ARRHYTHMIA IN CHILDREN AND ADOLESCENTS WITH HYPERTROPHIC CARDIOMYOPATHY: INCIDENCE AND RELATION TO PROGNOSIS.
William J. McKenna, MD, John Deanfield, MB, Rodney Franklin, MB, Shirley Krikler, Shaughan Dickie, DCR. Hammersmith Hospital, R.P.M.S., London, U.K.

The annual mortality from sudden death is approximately 5 per cent in children and adolescents with hypertrophic cardiomyopathy (HCM). Clinical, ECG and hemodynamic characterisation does not identify those who are at particular risk. To determine the incidence and relation of arrhythmia to prognosis we have performed prospective 48 hour ECG monitoring in 36 consecutive patients with HCM: 3 were infants (<1 year), 17 were 1-14 and 16 were 15 to 21 years of age. On the initial 48 hour ECG monitoring all were in sinus rhythm, none had ventricular tachycardia (VT), one had more than 250 ventricular extrasystoles per day, 3 had episodes of supraventricular tachycardia and another had reentry atrioventricular tachycardia associated with overt preexcitation. The patients were followed 1-6, median 2 years from the initial 48 hour ECG. In 12 patients, 23 additional 48 hour ECG's were performed: two had VT, one developed atrial fibrillation but no other new arrhythmias were detected. Twenty eight received beta blockers, 2 had verapamil and the child with the Wolff-Parkinson-White syndrome had amiodarone. Four patients died suddenly, another was resuscitated from out of hospital ventricular fibrillation and the only child to undergo myectomy died post-operatively. None of the patients who died had arrhythmias during 1-7, median 3 days of ECG monitoring. In contrast to adults, arrhythmias are uncommon in children and adolescents with HCM and are not a marker of those at particular risk of sudden death. This suggests that in children with HCM the initiating event of sudden death is more likely to be an acute hemodynamic alteration than an arrhythmia.

PROGRAMMED VENTRICULAR STIMULATION IN PATIENTS WITH DILATED CARDIOMYOPATHY WITHOUT SYMPTOMATIC ARRHYTHMIAS.
Sunil Das, M.D., Fred Morady, M.D., F.A.C.C., Lorenzo DiCarlo, M.D., Jeffrey Baerman, M.D., Ryszard Krol, M.D., Michael DeBuitleir, M.D., Barry Crevey, M.D. University of Michigan, Ann Arbor, Michigan.

A high incidence of sudden death (SD) in patients with dilated cardiomyopathy (DCM) coupled with our inability to predict its occurrence, prompted this prospective study using programmed ventricular stimulation (PVS). Twenty-two pts, 14 males, 8 females, mean age 40.7 yrs, fulfilling strict criteria for the diagnosis of DCM without symptomatic arrhythmias underwent PVS with 1-3 extrastimuli at 2 right ventricular sites, 24-hour Holter monitor (N=20), rest radionuclide left ventriculography (RNLVEF, N=22) hemodynamic measurements (N=21), and myocardial biopsy (N=16). In 7 pts (Gr I) sustained (4) or non-sustained (3) ventricular tachycardia was induced. In 15 pts (Gr II) VT was not induced. No significant differences were noted between Gr I and Gr II pts in the following parameters: Age: 40.7 vs 40.8; NYHA class: 3 vs 2.9; highest Lown arrhythmia class: 3.3 vs 3.1; RNLVEF: 27.6 vs 22.5; pulmonary capillary wedge pressure: 14.4 vs 21.2 mm Hg; cardiac index: 2.5 vs 2.4 l/mm/m^2. The degree of histologic fibrosis in the myocardial biopsy specimens in each group appeared similar. There were 3 SDs over a mean follow up of 8.6 (range 1-19) months, 1 in Gr I and 2 in Gr II; 1 additional death in Gr II was due to congestive heart failure. Thus, there is no correlation between inducible VT and other parameters including functional class, arrhythmia class, hemodynamic, degree of myocardial fibrosis, and incidence of SD during follow up in pts with DCM. The lack of inducible VT in these pts without symptomatic arrhythmias does not preclude SD during follow up.

Wednesday, March 12, 1986
4:00PM-5:00PM, Room #267
Pericardium: Physiology and Pathophysiology

REGIONAL VARIATION IN PERICARDIAL CONTACT PRESSURE.
Brian Hoit, M.D., Wilbur Lew, M.D., F.A.C.C. and Martin LeWinter, M.D., F.A.C.C., VAMC and Univ of California San Diego, San Diego, CA.

Based on studies performed with open ended catheters, it has been assumed that pericardial pressure is uniform over the surface of the heart. Recently, however, it has been shown that flat balloons more accurately reflect the pericardial "contact" pressure (PCP) between parietal and visceral pericardium. Accordingly, we used flat balloons in eight open chest dogs to determine if there are regional variations in PCP. PCP was measured simultaneously at two non-dependent sites (lateral RV and LV) while cardiac volume was varied by dextran infusions. Ventricular end-diastolic PCP (EDPCP) and mean PCP (PCP) at selected mean left atrial pressures (LAPs) were as follows (mmHg):

LAP	EDPCP-LV	EDPCP-RV	PCP-LV	PCP-RV
6±1(SD)	-0.4±1.1	-0.8±1.5	-0.6±1.4	-1.4±2.0
13±1	4.0±2.0	1.6±1.9	2.5±2.7	0.5±2.5
20±1	9.1±2.4 *	4.3±2.3	6.2±3.5 *	1.5±2.4

* LV>RV pressure at p<.05

These variations in PCP remained after severing the pericardial diaphragmatic attachments or turning the dog such that one or the other balloon was dependent. To further delineate the regional distribution of PCP, we positioned a single balloon sequentially at multiple ventricular sites. PCP was highest over the posterior and lateral LV, declined over the anterior LV and septum, and remained low over the anterior, lateral and posterior RV. We conclude that in the dog, PCP varies over the surface of the ventricles as cardiac volume increases, being highest over the lateral and posterior LV. These results suggest that the influence of the pericardium on ventricular filling is non-uniform and more complex than previously appreciated.

CORONARY ARTERY BLOOD FLOW DURING CARDIAC TAMPONADE IN THE CONSCIOUS DOG MEETS MYOCARDIAL REQUIREMENTS.
Gregory A. Bernath, M.D., Terrence L. Cogswell, M.D., Lawrence E. Boerboom, Ph.D., Donna Peterson, B.S., Dennis Janzer, M.S.B.E., H. Sidney Klopfenstein, M.D., Ph.D., Medical College of Wisconsin and Zablocki VA Medical Center, Milwaukee, Wi.

Coronary artery blood flow (CABQ) and left ventricular external work decrease dramatically during cardiac tamponade (CT) in conscious and anesthetized dogs. Since the hemodynamics of CT in anesthetized and recuperating animals differ from that normally seen, we used conscious dogs who had completely recovered from surgery to test the hypothesis that the decline in CABQ during progressive CT is a result of decreased myocardial requirements. Seven dogs were used to measure arterial and coronary venous O_2 content, lactate and pyruvate levels, as well as cardiac output (electromagnetic flowmeter) and regional myocardial blood flow (radionuclide - labeled microspheres) during CT induced by intrapericardial saline infusion.

	LV-MVO_2 (ml O_2/gm/min)	LV-CABQ (ml/min/gm)	LV endo/epi	Lactate/ Pyruvate
Baseline:	1.26±0.14	1.26±0.13	1.41±0.09	7.56±0.9
Decomp:	0.74±0.11*	0.53±0.06*	1.37±0.09	7.78±1.4

Baseline = empty pericardium; Decomp = decline in mean blood pressure to 70% of baseline level. Means ± S.E.M.; * = p < .05 versus baseline.

The decline in cardiac work during CT is associated with a decrease in LV-MVO_2 and despite a reduction in LV-CABQ, no change in LV endo/epi or coronary venous lactate/pyruvate ratios. This suggests that the decline in CABQ seen in conscious dogs during CT is appropriate to the needs of the myocardium and is not responsible for the changes observed in cardiac work.

DOPPLER ECHOCARDIOGRAPHY IN CONSTRICTIVE PERICARDITIS AND CORRELATION WITH COMPUTED TOMOGRAPHY AND PATHOLOGY.
Natesa Pandian, M.D., Jamil Kirdar, M.D., Jeffrey Isner, M.D., FACC, Julius Gardin, M.D., FACC, Kevin McInerney, Marjory Caldeira, David Fulton, M.D., FACC, Liv Hatle, M.D., FACC. Tufts-New England Medical Center, Boston, MA.

To assess the utility of Doppler echocardiography (DE) in constrictive pericarditis (CP) we used DE in 8 pts with clinical and hemodynamic evidence of CP, proven later by surgery. Morphologic measurements of the excised pericardium were made in all pts. In 6/8 pts, pericardial thickness was measured by computed tomography (CT) preoperatively. From DE mitral flow recordings we obtained early peak filling velocity (E), late peak filling velocity (A), E/A ratio, duration of early filling and % diastolic filling (%DF) from normalized diastolic filling curves. In addition we measured the maximal %Δ in velocity during respiration (Resp %ΔV). These were compared to data from 8 normals. Results: ($\bar{x}$±SD)

	Normals	CP	p
E m/sec	0.6±.08	0.86±.26	<.05
A m/sec	0.44±.07	0.28±.08	<.05
E/A ratio	1.36±.14	3.0±1.3	<.01
E duration millisec	274±38	183±27	<.01
%DF at 40% diastole	53±4	69±4	<.01
%DF at 50% diastole	58±3	77±6	<.001
%DF at 60% diastole	62±5	85±4	<.001
Resp %ΔV	16±4	99±67	<.01

DE findings consistent with increased early filling were present in each pt. CT showed thickened pericardium in all 6 pts who had CT (range 3-7mm). CT measurements were identical with morphologic measurements. We conclude that DE can reliably detect the characteristic filling abnormalities in CP. With accurate CT measurement of pericardial thickness, the combination of DE and CT can provide definitive non-invasive diagnosis of constrictive pericarditis.

COMPARATIVE EFFECTS OF PERICARDIECTOMY ON LEFT AND RIGHT VENTRICULAR DIASTOLIC PRESSURE-LENGTH RELATIONS.
Deodato Assanelli, M.D., Wilbur Lew, M.D., F.A.C.C., Martin LeWinter, M.D., F.A.C.C. VAMC and Univ of California San Diego, San Diego, CA.

The pericardium is known to restrain filling in the LV in the dog, but less is known about its effects on RV filling. Accordingly, we used sonomicrometers to measure segmental lengths (SL) in the RV inflow (IT) and outflow tracts (OT) and the LV free wall in six open-chest dogs. End-diastolic pressure (EDP) was varied with dextran infusions and vena caval occlusions before and after pericardiectomy. RV and LV filling were characterized by linear fits of ln EDP-SL data and determining the slope and the SL at EDP 1 mmHg. After pericardiectomy, the slope of the ln EDP-SL relationship did not change in the LV, but decreased in the RV IT (.94±.64[sd] vs .48±.29 mm/mmHg, p<.02) and RV OT (.93±.48 vs. .67±.4± mm/mmHg, p NS). After pericardiectomy, the SL at EDP 1 mmHg increased by 10±6% (p<.05) in the LV, but did not change in the RV IT or OT. In an additional dog, the RV and LV septal-lateral chord dimensions were measured with similar results, i.e. after pericardiectomy, the slope of the ln EDP-chord dimension did not change in the LV but decreased markedly in the RV. The ln EDP-SL data was also used to calculate the "effective" pericardial pressure over the RV and LV. Although the "effective" pericardial pressure did not differ between the RV and LV, the pericardium accounted for a significantly larger proportion of RVEDP than LVEDP at EDP above 2-3 mmHg. We conclude that the pericardium has qualitatively different effects on the RV and LV end-diastolic pressure-length relations and that the pericardium accounts for a larger proportion of the RV than LV end-diastolic pressure at all but low cardiac volumes.

Wednesday, March 12, 1986
2:00PM–3:30PM, Room #268
Myocardial Infarction—Experimental: Reperfusion

CORONARY RESERVE AFFECTS MYOCARDIAL BLOOD FLOW DISTRIBUTION AFTER REPERFUSION.
Makoto Akaishi, M.D., William S. Weintraub, M.D., F.A.C.C., Ricky M. Schneider, M.D., F.A.C.C., Lloyd W. Klein, M.D., F.A.C.C., Jai B. Agarwal, M.D., F.A.C.C., Richard H. Helfant, M.D., F.A.C.C., Mid-Atlantic Heart & Vasc Institute, Presbyterian-U of PA Med Ctr, Philadelphia, PA.

To determine the significance of underlying coronary stenosis on myocardial blood flow (MBF) after total coronary occlusion (TCO), MBF was measured 30 sec and 30 minutes after reperfusion (Rep) following 15 minutes TCO in dogs with carotid to left anterior descending coronary arterial cannulation. Group 1 (G-1) comprised 6 dogs with critical coronary stenosis (CCS) with no resting dysfunction, no deficit of resting flow but minimal reactive hyperemia (RH) (35±7%, reduced from 183±59%); group 2 (G-2) comprised 5 dogs with patent coronary artery (RH=133±31%). MBF(ratio to normal zone) before, during TCO and after Rep (* p<0.02 vs G-1):

		Pre-TCO	TCO	30"-Rep	30'-Rep
Endo-MBF	G-1	.94±.09	.05±.01	.50±.08	.43±.22
	G-2	1.13±.48	.06±.07	2.07±.86*	.94±.24*
Epi-MBF	G-1	.95±.26	.26±.17	1.75±.70	.84±.21
	G-2	1.05±.22	.27±.18	3.78±1.48*	.90±.13

In G-2, post-ischemic hyperemic flow was observed in both subendocardium and subepicardium immediately after Rep, returning to normal 30 min after Rep. In G-1 subendocardial underperfusion lasted for 30 minutes after Rep. Regional segment shortening recovered to 54±16% of control at 30 min-Rep in G-2 and 33±27% in G-1. There was no difference in hemodynamics between the two groups. Conclusions: Underlying coronary stenosis limiting coronary reserve, without deficit in resting flow and function, induces prolonged subendocardial underperfusion after Rep. Patients with underlying stenosis are disposed to longer ischemia after Rep.

PROSTACYCLINE-INDUCED PROTECTION OF ISCHEMIC MYOCARDIUM IN RABBITS WITH CORONARY ARTERY OCCLUSION-REPERFUSION.
M. Chiariello M.D., F.A.C.C., P. Golino M.D., M. Cappelli-Bigazzi M.D., M. Salvatore M.D., S. Quattrin M.D., P. Perrone-Filardi M.D. Dept. of Internal Medicine, 2nd School of Medicine, University of Naples, Italy.

To assess whether prostacycline (P) is able to partially prevent myocardial damage after coronary artery occlusion (CAO) followed by reperfusion (R), 19 rabbits underwent CAO for 1 hr and reperfusion for 5 hrs. One minute after CAO, $2X10^5$ ^{99}Tc-labeled albumin microspheres were injected into the left atrium for later assessment of the hypoperfused zone, (HZ), i.e., the area at risk of infarcting. Fifteen min after CAO, the animals were randomly assigned to a control (n=9) and a treated group (n=10, T) receiving an infusion of a stable analogue of P, ZK36374, 1.2 mcg/kg/min for 6 hrs. Blood samples were drawn immediately before and 5 hrs after starting the treatment to measure platelet function. Arterial pressure and ECG (lead aVF) were continuosly monitored . At the end of the experiment, infarct size (IS) was calculated by planimetry on left ventricular slices stained by triphenyltetrazolium chloride. HZ was assessed planimetrically by autoradiography of the same slices. CAO + R produced similar HZs in both groups, being 30±3% and 32±4% of left ventricle in C and T, respectively. However, IS, i.e., the percentage of HZ that actually evolved to necrosis, was dramatically smaller in T than C, 47±4% vs. 98±9% respectively (p .001). This represents a 55% salvage of jeopardized tissue. ZK36374 provoked a complete inhibition of platelet function, as demonstrated by an absolute unresponsiveness of platelets to aggregating agents in vitro but did not change hemodynamics. Thus, ZK36374 protects ischemic myocardium from reperfusion damage: this beneficial action may be mediated by the effect of the drug on platelet function.

CHRONIC MODIFICATIONS OF DIETARY SODIUM ALTER VENTRICULAR DILATATION IN RATS WITH MYOCARDIAL INFARCTION.
Peter J. Gaudron, M.D., Janice M. Pfeffer, Ph.D., and Marc A. Pfeffer, M.D., Ph.D., F.A.C.C. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Ventricular size is an integral component of ventricular function and a major prognostic factor for survival in patients with heart failure. We have observed progressive ventricular enlargement in rats with moderate and large experimental myocardial infarctions (MI) even after the histologic resolution of the MI. To determine whether modifications in dietary sodium intake could alter ventricular enlargement post-MI, sham operated (C) and infarcted (20 to 40% of LV circumference) rats were placed on either a low (L, 0.04%), regular (R, 0.5%), or high (H, 3.6%) Na diet two weeks post-MI and followed for a period of 8 additional weeks. Rats were anesthetized with ether for assessment of hemodynamics and subsequent passive LV pressure-volume relations. In C rats, Na diets did not alter hemodynamics or LV size. In contrast, even though hemodynamics were not altered by diet in MI rats, LV size (volume index at 5 and 20 mmHg distending pressure) increased in relation to dietary sodium intake.

	n	MAP (mmHg)	CI (ml/kg)	LVEDP (mmHg)	Vol_5* (ml/kg)	Vol_{20}* (ml/kg)
L	14	112±4	226±15	9±1	1.23±0.08†	1.89±0.13
R	13	109±5	239±13	7±1	1.44±0.12	2.14±0.15
H	16	105±4	228±12	8±1	1.60±0.10	2.39±0.12

(*variable altered by diet, ANOVA p<0.05, † p<0.05 versus H).
Thus, this study demonstrates that the process of ventricular dilatation (remodeling) post-MI can be modified by dietary manipulation. The attenuation of ventricular dilatation may be a key factor in preventing late-onset heart failure post-MI.

PROMPT DETECTION OF MYOCARDIAL REPERFUSION BY ANALYSIS OF CREATINE KINASE ISOFORMS IN PLASMA
Stephen R. Devries, M.D., Burton E. Sobel, M.D., F.A.C.C., and Dana R. Abendschein, Ph.D., Washington University School of Medicine, St. Louis, Missouri

Myocardium undergoing infarction liberates the tissue isoform of CK MM isoenzyme (MM_A). To determine whether sudden washout of MM_A reflected by altered plasma CK isoform profiles is a more sensitive criterion for early noninvasive detection of reperfusion than conventional enzyme assay, coronary occlusion was induced in 11 conscious dogs, released 2 hr later in 6 dogs, with reflow verified with a previously implanted Doppler flow probe. Isoforms were analyzed in serial plasma samples with a non-denaturing, quantitative, chromatofocusing procedure developed and validated preiously. With reperfusion, the percentage of total CK activity attributable to MM_A (MM_A%) peaked at 54 ± 6% (SD) within 30 min (2.5 hr after occlusion). In the absence of reperfusion, peak MM_A% occurred much later (4.8 ± 1.3 hr after occlusion). The rate of increase of plasma MM_A% was ten-fold greater within 30 min after reperfusion (1.28 ± .45% min^{-1}) than in its absence (.12 ± .03% min^{-1}) ($p < .002$) -- an augmentation not depenent on absolute CK activity in plasma or infarct size measured histochemically 24 hr after occlusion ($r = .03$). Comparable rates of increase of MM_A% occurred in 6 other dogs subjected to reperfusion either 1 hr (n = 3) or 3 hr (n = 3) after coronary occlusion (1.44 ± .42% min^{-1} and 1.15 ± .29% min^{-1}). Because reperfusion elicits rapid rates of increase of MM_A% in plasma, analysis of MM_A% in only two blood samples obtained within 30 min permits prompt, definitive, and noninvasive detection of reperfusion.

Mechanical Thrombolysis in Acute Canine Coronary Thrombosis. D. Dennis Hansen, David Auth, Rudy Vracko, James L. Ritchie. Seattle VA Hospital and University of Washington, Seattle, WA.

Coronary thrombosis precipitates most acute myocardial infarctions. We studied a new thrombectomy catheter system with a rotating guidewire capable of lysing acute arterial thrombus. The TC consists of an .008 or .006" diameter wire with a steerable .025" diameter platinum tip. Rotation of the wire (6000 rpm) within the thrombus entwines fibrin tightly about the shaft, allowing its withdrawal. Cellular elements are released into the circulation and the clot is effectively lysed. In vitro, the rotating TC was passed through human thrombus in a test tube. Each pass removed 22±8 mg of material (n=37), mostly fibrin. Thrombi were liquified when 10% of their weight was removed. One gram of clot could be liquified with 5.5±.07 (n=4) passes with the device. Particle sizing of the liquified thrombus showed only single red cells and clumps of red cells under 10 microns in diameter. In vivo, acute coronary thrombi were produced in 10 open chest dogs by crush arterial injury and injection of thrombin. The TC was then passed through the clot with an 8 french angioplasty introducer. Initial flow was restored in all cases with one pass. An average of 2.2±1.4 passes were performed. Fibrin was removed in 7 of the 10 arteries. Flow was graded by the TIMI scoring system (0=no flow, 3=nl flow). TIMI grade 3 flow was achieved in 9 of 10 arteries and the residual diameter stenosis was estimated to be 22±22%. Residual thrombus was histologically present in 80%. One early perforation occurred.

We conlcude that a new rotational TC can easily restore flow in acutely thrombosed canine coronary arteries.

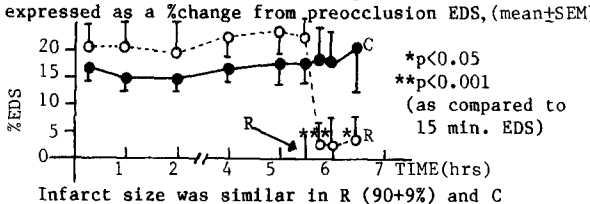
Wednesday, March 12, 1986
4:00PM–5:00PM, Room #268
Laser Technology

ESTIMATION OF ARTERIAL WALL THICKNESS AND DETECTION OF ATHEROSCLEROSIS BY LASER INDUCED ARGON FLUORESCENCE. Michele Sartori M.D., Philip D. Henry, M.D., F.A.C.C., Robert Roberts M.D., F.A.C.C. Baylor College of Medicine, Houston, TX. Robert P. Chin B.S., Michael J. Berry P.h.D. Rice University, Houston, TX.

Vascular wall perforation represents the main complication of laser angioplasty, and the determination of wall thickness is critically important for the safe ablation of atherosclerotic lesions. To assess whether the interaction of laser with arterial tissue provides information about arterial wall structure including changes in wall thickness, we determined the argon fluorescence spectra of 16 normal (N) and 17 atherosclerotic segments (A) from human aortas and coronary arteries. The arterial walls were excited at low power (100 microwatts) with an argon ion laser at a wavelength of 459nm. Three emission peaks (P) were identified at 530, 550 and 600 nm. The ratio (R) of the peak at 530nm to the peak at 550nm differed significantly between N and A, values averaging 1.55±0.27 (SD) and 1.09±0.17 ($p<0.001$). Excluding lesions with a low R-value (<0.9) due to dense calcification there was a significant negative correlation between R and intimal thickness measured by light microscopy of frozen tissue ($r=-.747, p<0.001$). Thus, in addition to its ablative properties at high energy, low energy argon laser may be used to characterize arterial structure. The recording of argon laser excitation fluorescence spectra provides information about 1) the thickness of the normal and atherosclerotic arterial wall, and 2) the presence or absence of atherosclerotic lesions.

LATE MYOCARDIAL REPERFUSION CAN BE BENEFICIAL WITHOUT INFARCT REDUCTION. Prasad S. Gadde, M.D., Rita D.Swinford, B.S., Andrew T. Smyth, B.S., Bennett J. Shatkin, M.D., Teresa A. Smith, Peter F. Cohn, M.D., F.A.C.C., Edward J. Brown, Jr., M.D., F.A.C.C., SUNY Health Sciences Center, Stony Brook, N.Y.

It is generally believed that to be beneficial, reperfusion must be performed early enough post infarction to salvage ischemic tissue. However, a recent clinical trial demonstrated improved survival in patients undergoing coronary reperfusion despite no reduction in infarct size (IS). This improvement could be explained on the basis of less myocardial expansion. To investigate this hypothesis, acute dogs were randomized to 6½ hrs. of left anterior descending coronary occlusion(C) or 5½ hrs. of occlusion and 1 hr. reperfusion(R). Pairs of ultrasonic crystals were placed circumferentially in the midmyocardium of the infarct and normal zones. Area at risk was determined by an injection of thioflavin-S prior to sacrifice. IS was determined by triphenyltetrazolium chloride incubation and was expressed as a % of the area at risk. Infarct end diastolic crystal separation (EDS) in R (n=4) and C dogs (n=4) is shown and expressed as a %change from preocclusion EDS, (mean±SEM):



Infarct size was similar in R (90±9%) and C animals (97±1%). Thus, reperfusion results in a decrease in myocardial expansion even when there is no salvage of myocardial tissue.

EXCIMER LASERS FOR ANGIOPLASTY: COMPARISON OF KrF AND XeCl AND MECHANISM OF TISSUE ABLATION
Martin B. Leon, MD, FACC, David J. Underhill, MD, Paul D. Smith, PhD, James R. McDonald, PhD, Stephen E. Epstein, MD, FACC, Richard E. Clark, MD, FACC, Robert F. Bonner, PhD, NHLBI, Bethesda, Md.

Although Excimer lasers (Ex) have been shown to produce efficient tissue ablation without surrounding thermal injury, the mechanisms of ablation and effects of different wavelengths are poorly understood. Therefore, human cadaver coronary arteries (n=8, target sites=114) were exposed to KrF(248nm) and XeCl(308nm) in air at varying pulse energy densities (ED) and power densities (PD). For both Ex, infrared thermography and ocular micrometry demonstrate that increasing ED above the ablative threshold produces linear changes in surface temperature and crater depth suggesting that tissue cutting is dependent upon linear absorption of ultraviolet light by protein and nucleic acids. Eccentric craters with lateral clefts created by shock waves from non-linear plasma formation were observed at higher PD (1 GW/cm^2) which is near the damage threshold of commercial fibers. Important differences were found among Ex; ED, PD, and peak surface temperature elevations at the ablative threshold were all significantly lower with KrF (5 mJ/mm^2, .04 GW/cm^2, and 6°C) than with XeCl (18 mJ/mm^2, .11 GW/cm^2, and 12°C). Correspondingly, ablation efficiency was greater with KrF (.9mm^3/J) than with XeCl (.4mm^3/J). We conclude (1) Ex utilize the strong linear ultraviolet absorption of tissue for specific and predictable ablative effects, (2) superficial ablation can be achieved with Ex at PD below the damage threshold of quartz fibers, and (3) KrF is more efficacious than XeCl due to stronger protein absorption at 248nm. These studies help to clarify the design parameters necessary for precise intra-arterial microsurgery.

CONTROLLED ABLATION OF ATHEROSCLEROTIC PLAQUE: EXPERIMENTAL AND THEORETICAL DOSIMETRY

Robert M. Cothren, M.S., Carter Kittrell, Ph.D., Robert L. Willett, M.D., Edward G. Malk, Ph.D., Corinne Bott-Silverman, M.D., John R. Kramer, M.D., F.A.C.C., Michael S. Feld, Ph.D., MIT Spectroscopy Laboratory, Cambridge, MA

Understanding the laser ablation process is crucial for establishing conditions for efficient removal of atherosclerotic plaque with minimal damage to adjacent tissue. A simple theory of thermal tissue removal has been developed which predicts the steady-state ablation velocity (v) and tissue temperature profile as functions of the thermal tissue properties, penetration depth (D) of laser light into tissue, and the laser power (P) and beam diameter (d). Both thermal diffusion and optical scattering are included. Results were compared with accurate dosimetry studies taken in fiberous plaque cadaver artery using blue-green argon ion laser light. For example, for P=5W and d=1/4, 1/2, 3/4 and 1mm, we find experimentally that v=2.8, 2.7, 1.4 and 0.87 mm/sec, respectively. Using our measured value of D=0.38mm and assuming (thermal properties of water), these results are in good agreement with theory. The theory can thus be used to predict ablation velocities at new laser wavelengths and direct the user to the correct photon dose.

EXCIMER LASER ANGIOPLASTY: QUANTITATIVE COMPARISON OF ArF, KrF & XeF ENERGY ON NORMAL AND ATHEROMATOUS TISSUE.

Tim Bowker MB, Frank Cross MB, Philip Rumsby PhD, Malcolm Gower PhD, Philip Poole-Wilson MD, Kim Fox MD, Stephen Bown MD and Anthony Rickards FACC.
The National Heart Hospital, London, England.

The risk of vessel perforation in laser angioplasty may be reduced by the use of pulsed u.v. excimer lasers, which destroy tissue by photo-ablation (a non-thermal mechanism of molecular disruption), without causing surrounding thermal damage to the residual non-vaporised arterial wall immediately subjacent to the laser crater.

To find which u.v. wavelength would be appropriate for the photo-ablation of atheroma, we quantified the effect of different energy densities of an excimer laser run at three different wavelengths - 193nm (ArF), 249nm (KrF) and 351nm (XeF), on samples of normal and of atheromatous human post-mortem aortic wall in which, craters were produced by delivering a train of 250 20ns pulses of the directly focussed beam at a repetition rate of 2.5 Hz. The range of energy densities used per crater were as follows - 56, 80, 101, 167, 238, 277, 350 and 555 J/sq.cm at both 193 and 249 nm, and 101, 167, 277 and 555 J/sq.cm at 351nm. Five craters were made in both normal and atheromatous samples at each wavelength and at each power density. A careful record was kept of the energy parameters used to produce each crater, the depths of which were then measured to the nearest 10 um.

At all three wavelengths crater depth was proportional to energy density, a plateau being reached at 160 J/sq.cm with 351nm, 350 J/sq.cm with 249nm and 270 J/sq.cm with 193nm. The gradient of the "dose-response" relationship was least steep at 351nm (0.125 um penetration per J/sq.cm of energy delivered), steeper at 193nm (0.62 um per J/sq.cm) and steepest at 249nm at which wavelength, each energy density consistently gave greater penetration into atheromatous tissue than it did into normal (1.13um per J/sq.cm & 0.71um per J/sq.cm respectively). Such an atheroma-selective effect was not seen at 193 or 351 nm. Indeed, with 249nm, at an energy density of 230 J/sq.cm, the gradient steepened further to 3.09um per J/sq.cm and 1.90um per J/sq.cm for atheromatous and normal tissue respectively. Thus of the three wavelengths, 249nm (KrF) appears appropriate for laser angioplasty, and is the pulsed excimer laser wavelength for which a fibre-optic intra-coronary delivery system should be developed.

Wednesday, March 12, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 4:00PM–5:00PM
Hall D, Georgia World Congress Center
Coronary Artery Disease—Clinical

COMBINED INTRACORONARY PROSTAGLANDIN E_1 AND STREPTOKINASE INFUSION IN ACUTE MYOCARDIAL INFARCTION.

Bim Sharma, M.D., F.A.C.C., Richard P. Wyeth, M.A., Gary E. Lane, M.D., Horacio J. Gimenez, M.D., Steve W. Hutchins, M.D., Joseph A. Franciosa, M.D., F.A.C.C., Univ of Arkansas for Medical Sciences, Little Rock.

Fourteen patients (pts; 13 males, mean 51 ± 14 yr) with acute myocardial infarction (MI) were studied within 5.0 ± 2.2 hr of the onset of chest pain. Ten pts (Gr A) received intracoronary (IC) prostaglandin E_1 (PGE_1) followed by IC streptokinase (SK) while four pts who failed to recanalize with IC SK were subsequently infused with IC PGE_1 (Gr B). In both groups IC SK was infused at a rate of 4,000 to 10,000 IU/min till thrombolysis occured or a total of 400,000 IU of SK. Infusion of PGE_1 began at a rate of 5 ng/kg/min and was increased by 5 ng/kg/min at 10 min intervals to a maximum of 20 ng/kg/min or until angiographic evidence of reperfusion. Prior to therapy all infarct related vessels were occluded. In both groups coronary angiography was repeated at 10 min intervals. In Gr A reperfusion was achieved in all 10 pts while in Gr B reperfusion occured in 2 of 4 IC SK failures. The total IC SK dose required for reperfusion was 118,000 ± 84,000 IU (range 0 to 250,000 IU) in Gr A while in Gr B both pts were recanalized with 20 ng/kg/min PGE_1 after failing to open with 400,000 IU of IC SK. There were no bleeding complications associated with this combined therapy, but one pt developed transient hypotension. This preliminary study indicates such combined therapy, IC PGE_1 with SK, is both safe and efficacious. The 100% recanalization rate when IC PGE_1 is followed by IC SK is greater than that reported with SK alone. Intracoronary PGE_1 merits further evaluation in acute MI.

SIGNIFICANCE OF POST INFARCTION ANGINA IN PATIENTS WITH SINGLE VESSEL DISEASE.

Louis Gleckel, M.D., Sheryl Wulkan, M.D., Jerome H. Koss, M.D., F.A.C.C., Monty M. Bodenheimer, M.D., F.A.C.C. Long Island Jewish Medical Center, New Hyde Park, NY.

While the prognosis of patients (pts) with angina and single vessel disease (SVD) is good, the prognosis of pts undergoing coronary angiography for post infarct angina (PIA) and found to have SVD is unclear. All of 40 consecutive pts with SVD (> 70% stenosis) catheterized for PIA within 3 mos of an MI were followed up after a mean of 39 mos (range 26-51 mos). Eight pts (20%) had subsequent morbid events including: 3 deaths, 1 from heart failure, right coronary artery (RCA) lesion and 2 suddenly, 1 left anterior descending (LAD) and 1 RCA; 1 successfully resuscitated sudden death RCA and 4 nonfatal myocardial infarctions (MI) (2 LAD, 1 left circumflex (LCX), 1 RCA). Of the 4 pts with recurrent MI, 3 were in the same vascular distribution. Another 4 pts had bypass (1 died) and 1 pt had successful PTCA. Of the 32 pts with no morbid events, 12 had LAD, 13 had RCA and 7 had LCX lesions. Left ventricular contraction was severely hypokinetic or akinetic in the subserved zone in 6/8 pts (75%) with morbid events and in 23/32 pts (72%) with no events. Thus: 1) Angina within 3 mos of infarction is associated with a high morbid event rate. (2) Neither the coronary vessel involved nor the severity of dysfunction in the subserved zone predicted outcome. 3) The benign prognosis associated with SVD does not apply to this group and more aggressive therapy may be warranted.

IMPAIRED ENDOTHELIAL-DEPENDENT CORONARY DILATION IN PATIENTS WITH CORONARY ARTERY DISEASE

Paul L. Ludmer, M.D., Andrew P. Selwyn, M.D., FACC, Richard R. Wayne, Gilbert H. Mudge, M.D., R.Wayne Alexander, M.D.,FACC, and Peter Ganz, M.D., Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Endothelial dysfunction underlies atherogenesis. Many vasodilators including acetylcholine (ACH) relax smooth muscle indirectly by stimulating the release by endothelium of relaxing factor(s). We tested the hypothesis that endothelial-dependent vasodilator function is also impaired in patients with coronary disease. We infused graded concentrations of ACH (final concentrations 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}M) and for comparison, nitroglycerin (TNG), a dilator without endothelial dependence, subselectively in the left anterior descending artery (LAD) of 7 pts with LAD stenosis and 2 normals. The responses were evaluated by quantitative coronary angiography with non-ionic contrast. In multiple segments of 2 normal coronary arteries, ACH caused a dose-dependent dilation from 1.62±0.48 mm (control) to 2.20± 0.70 mm (maximal ACH dose) ($p < 0.01$). In contrast, all 7 pts with LAD stenoses showed a dose-dependent constriction to ACH with temporary complete vessel occlusion in 4. A dose-dependent constriction to ACH occurred in the prestenotic coronary segment (1.86±0.25 to 1.06±0.63 mm maximal response, $p < 0.01$) and the stenotic coronary segments (1.01±0.12 to 0.52±0.48 mm, $p < 0.01$). Subselective LAD infusion of TNG (50 mcg) produced dilation ($p < 0.01$) in both normal and stenotic coronary arteries. Thus the paradoxical constriction by ACH of the atherosclerotic coronary artery together with the normal response to the direct smooth muscle dilator TNG implies the loss of normal endothelial vasodilator function in CAD. This impairment of endothelium-dependent relaxation may contribute to inappropriate coronary vasoconstriction.

CORONARY ATHEROSCLEROSIS AND PLATELET ACTIVATION IN ISCHEMIC HEART DISEASE: A NON-QUANTITATIVE LINK.

Raffaele De Caterina, M.D., Paolo Gazzetti, Annamaria Mazzone, M.D., Mario Marzilli, M.D., and Antonio L'Abbate, M.D., F.A.C.C., CNR Institute of Clinical Physiology, Pisa, Italy.

We evaluated the relationship between indexes of in vivo platelet activation (plasma β-thromboglobulin (BTG) and platelet factor 4 (PF4)) in 42 patients (pts) with Ischemic Heart Disease and 40 controls. Pts had one-week continuous ECG monitoring in absence of therapy, by which they were divided into 3 groups: A: active disease (>1 episode/day of spontaneous ischemia, n=9); B: rare spontaneous ischemia (<1 episode/day, n=17); C: inactive disease (n=16). Pts underwent 2 baseline blood samplings, coronary angiography, and 3 samplings while on effective oral nitrates and calcium antagonists. Compared to controls, group A pts had higher BTG and PF4 values (49.7±9.6 vs. 25.9±6.3 and 8.6±3.1 vs. 4.4±1.7, ng/ml, mean±SD, P<.001 and .05, respectively). Group C pts had normal values (22.9±8.1 and 4.6±2.8). Group B pts had intermediate values (29.0±11.2 and 6.0±3.8). The extent of coronary atherosclerosis (ATS) was similar in group A and C, however group C pts had a greater prevalence of severe (>90%) stenotic segments (12% vs. 6%). BTG and PF4 in group A became normal during therapy (29.3±11.1 and 5.5±3.2). We conclude that (1) the activity of the disease and not the extent or hemodynamic severity of ATS is positively correlated with platelet activation; (2) effective medical treatment normalizes platelet function.

EMPLOYMENT IN MEN WITH CORONARY DISEASE: EFFECTS OF DISEASE, PSYCHOLOGIC AND DEMOGRAPHIC FACTORS.

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To study the relative importance of extent of disease, psychologic and demographics upon employment in patients with coronary disease, we examined 818 men below 60 years of age. Employment status at the time of cardiac catheterization was related to clinical factors, psychological test results (Minnesota Multiphasic Personality Inventory, Zung Depression and Anxiety Scales, Type A interviews, Jenkin's Activity Survey) and demographics. Stepwise logistic multiple regression analyses were used to assess the relative importance of these factors.

Many single factors differed between the 234 (29%) men who were not working compared with the 584 (61%) who were. Non-working men had greater extent of disease (more coronary disease, lower ejection fractions, higher indices of angina, previous myocardial infarction and co-existing vascular disease). Non-working men were also more depressed and anxious, and had lower ego strength and higher hypochondriasis, but were no different in Type A behavior. Non-working men were also less educated but no different in age, or number of dependents.

By multivariable analysis, the most significant ($p<0.01$) independent predictors of non-working status were, in order, low education level, history of myocardial infarction, high levels of depression and high levels of hypochondriasis. We conclude that psychologic and social factors are strongly related to work status in patients with coronary disease, and may be more important than medical factors.

CIRCADIAN VARIATION OF SUDDEN CARDIAC DEATH

Paul L. Ludmer, MD, Gail Z. Alymer, James E. Muller, MD, FACC, Harvard Medical School, Boston, MA

A circadian rhythm (CR) in frequency of onset of non-fatal myocardial infarction (MI) has recently been demonstrated with a peak onset from 0600 to 1200 hours, a period when platelet aggregability (PA) is also increased. Sudden cardiac death (SCD) may be caused by PA which could have led to MI had the patient survived. We performed a retrospective review of the time of SCD. Data were compiled from death certificates of a random sample (n=1063) of the 8223 individuals presumed to have died from "MI" (ICDA Code #410) in Massachusetts in 1983. SCD was defined as death occurring without prodromata or <1 hour after onset of symptoms. The percent of deaths during quarters of the day are:

TIME:	0-6	6-12	12-18	18-24 hours
Deaths from "presumed MI" (n = 1063)	22%	30%*	26%	22%
Total SCD (n = 632)	22%	31%*	27%	21%
In hospital SCD (n = 245)	19%	31%*	26%	24%
Out of hospital SCD (n = 387)	24%	31%*	27%	19%

*** = $p < 0.001$ vs. mean of other three 6-hour periods**

It is unlikely that the CR is an artifact produced by delayed recognition of SCD during sleep since it was observed in individuals in whom <1 hour elapsed from symptom onset to death. Thus, there appears to be a marked circadian variation in frequency of SCD which parallels that of MI and PA. If prospective study confirms the existence of this CR, the pathogenesis of SCD and its relation to MI would be better understood, and new approaches to prevention could be designed.

PLASMA CONCENTRATION OF IMMUNOREACTIVE ATRIAL NATRIURETIC FACTOR (IR-ANF) IN PATIENTS WITH CORONARY ARTERY DISEASE

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To investigate whether plasma concentrations of IR-ANF are increased in patients with coronary artery disease, aortic blood samples were obtained in 110 consecutive patients undergoing diagnostic coronary angiography. IR-ANF was measured by a specific radio-immunoassay for human plasma (Biochem. Biophys. Res. Comm., 1985; 128: 1350-1357) and expressed as picograms (pg) per milliliter (ml). IR-ANF plasma concentrations were significantly higher in 98 patients with coronary artery disease (≥70% reduction in lumen diameter of coronary vessels) than in 12 subjects with atypical chest pain, normal coronary anatomy and normal left ventricular (LV) function (131±55 vs 102±37 pg/ml, p<0.01). In patients with coronary artery disease, 5 of 18 baseline clinical and angiographic variables were associated with increased plasma concentrations of IR-ANF:

	No. of patients	IR-ANF (pg/ml)	p value
Hypertention - No	64	119±48	
Yes	34	142±56	0.0329
LVEDP ≤14 mmHg	53	109±35	
>14 mmHg	45	148±60	0.0001
EF ≥0.50	81	119±44	
<0.50	17	164±70	0.0012
No. diseased V ≥50%-1	31	99±31	
2+3	67	154±55	0.0001
No. diseased V ≥70%-1	51	112±44	
2+3	47	144±55	0.0022

EF=ejection fraction, LVEDP=LV end diastolic pressure; V=vessels; ±=mean ± S.D.

The stepwise logistic regression analysis identified multivessel disease ≥50% or ≥70% and abnormal LVEDP as predictors of increased plasma IR-ANF concentrations (≥115 pg/ml). We conclude that plasma IR-ANF concentrations are frequently increasesd in patients with coronary artery disease and that, in addition to left ventricular dysfunction, the severity and extent of coronary disease contributes to this elevation.

EFFECTS OF SEVERE MYOCARDIAL ISCHEMIA DURING CORONARY OCCLUSION ON SYNTHESIS OF THROMBOXANE A_2 IN HUMAN CORONARY CIRCULATION

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To examine whether the increase in plasma thromboxane B_2 (TXB_2) is primary or secondary significance in patients with ischemic heart disease, plasma level of TXB2 in great cardiac vein (GCV) were determined before and immediately after occlusion of anterior descending coronary artery with balloon catheter in ten patients who underwent percutaneous coronary angioplasty. Blood samples were obtained simultaneously from the artery and the GCV for determination of lactate and TXB_2 concentration, using enzymatic method and radioimmunoassay respectively. Efflux of TXB_2 was calculated as the product of concentration of arterio-GCV TXB_2 difference and GCV flow measured by continuous thermodilution technique on the seccond occlusion. One minute occlusion of proximal portion of anterior descending coronary artery induced ST-T segment elevation in chest leads of ECG and marked decrease in lactate extraction ratio(LER), which reveal severe ischemia in the anterior myocardium. However, plasma TXB_2 level in GCV and TXB_2 efflux did not change as follows.

	before	after
TXB_2 in GCV (pg/ml plasma)	263 ± 67	253 ± 73
TXB_2 efflux (ng/min plasma)	6.7 ± 2.6	6.1 ± 2.4
LER (%)	23 ± 19	-10 ± 9 *

(mean ± SD, *P<0.01 vs before, LER = ((arterial lactate - GCV lactate)/arterial lactate) x 100)

We conclude that TXB_2 is not the secondary substance which was induced by myocardial ischemia, but may be primarily derived from the altered platelet function in patients with ischemic heart disease.

CIGARETTE SMOKING-INDUCED RELEASE OF β-THROMBOGLOBULIN FROM PLATELETS IS NOT INHIBITED BY DIPYRIDAMOLE AND ASPIRIN

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Platelet activation seems a likely mediator of the association of cigarette smoking with coronary artery disease (CAD) morbidity and mortality. The purpose of this study was to learn whether cigarette smoking caused release of β-thromboglobulin from platelets of men with CAD and whether dipyridamole and aspirin prevented release. This random-order, double-blind crossover study compared the effects of placebo, dipyridamole, and dipyridamole plus aspirin on smoking-induced release of β-thromboglobulin. Each of 12 male habitual smokers with (CAD) took dipyridamole 75 mg and aspirin 324 mg, dipyridamole 75 mg and placebo for aspirin, or a placebo for each drug t.i.d. for 1 week before each of 3 20-min periods (2 weeks apart) of smoking 2 Winston King Size cigarettes after 12 hr of abstinence. During each period there was an increase ($p = 0.02$ or less) in the mean plasma concentration of β-thromboglobulin (determined by radioimmunoassay) of 11 to 23% and nicotine (determined by gas chromatography). Dipyridamole alone and in combination with aspirin had no significant effect on the mean presmoking value of or the mean smoking-induced change in either variable. After smoking, correlation coefficients between concentrations of nicotine and β-thromboglobulin after taking both placebos, dipyridamole and placebo for aspirin, and dipyridamole and aspirin were 0.85 ($p < 0.001$), 0.60 ($p < 0.05$) and 0.96 ($p < 0.001$) respectively. We conclude that smoking consistently increased the mean plasma concentration of a platelet-specific α-granule protein and that this release was not inhibited by dipyridamole and aspirin.

A LARGE PEDIGREE WITH MIXED ADVERSE LIPOPROTEIN LEVELS AND A PREDISPOSITION TO CARDIOVASCULAR DISEASE: BOGALUSA HEART STUDY.

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Two hundred (121 females, 79 males) living pedigree members of a large kindred (N=420) were examined for cardiovascular disease (CVD) risk factors and their correlates. Mixed adverse changes of lipoproteins (LP) were found consisting of elevated LDL-C and VLDL-C, and low HDL-C in both sexes, resulting in extremely high LDL-C/HDL-C ratios. CVD risk factor abnormalities were reported in nearly 45% of those examined. While over 10% of this total kindred had a history of myocardial infarction (MI), only about 3% of screened pedigree members had previous history of MI. Within this pedigree, 34% of members were first degree relatives of MI victims. Also, women appeared to be less susceptible to the atherogenic phenotype of elevated LDL-C and decreased HDL-C than men, as evidenced by the absence of LDL-C abnormalities among men (but not women) living into or past the fifth decade of life. In addition, increasing levels of LP risk were found as the degree of genetic relationship increased to a pedigree member with MI. These data indicate that the phenotypic effect of elevated LDL-C, VLDL-C and decreased HDL-C yields persons especially susceptible to CVD (e.g., heart, cerebral, kidney, diabetes). Genetic analysis suggests the possibility of a major gene segregating in this pedigree to produce this LP phenotype and that it may be common within families where CVD is aggregating.

PATIENTS WITH SYNDROME X: EFFECTS OF CORONARY DILATORS ON EXERCISE CAPACITY AND MYOCARDIAL OXYGEN SUPPLY.

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Patients (pts) with effort related angina, angiographically normal coronary arteries and no evidence either of epicardial artery spasm or myocardial hypertrophy, i.e. pts with syndrome X,have been suggested to be affected by an inappropriate constriction of coronary resistive vessels during stress and/or tachycardia. Thus coronary dilation could result in increased oxygen supply and exercise duration. Accordingly we assessed the effects of isosorbide dinitrate (ID), verapamil (V) and iloprost(I),a stable prostacyclin analog,on exercise capacity,coronary blood flow (CBF) and resistance (CR) in 15 pts with the above set of findings and exercise stress testing limited by chest pain. Supine bicycle ergometer testing(25 W increments every 2 min)was performed before(control)and during vasodilation which was obtained in 5 pts with V(10 mg i.v.),in 5 with ID(10 mg s.l.)and in the remaining with I (6 ng/kg per min for the entire test). Interventions were randomized in a single blind fashion. Compared to control, V significantly ($p < .001$ paired-t-test) prolonged exercise duration ($\bar{x}\pm SD$: 510±74 vs 364±67 sec) and time to onset of 0.1 mV ST↓ (393±50 vs 237±36 sec). Its administration resulted also in increased ($p<.005$) CBF (137±31 vs 95±28 ml/min) and decreased ($p<.005$) CR (0.86±0.15 vs 1.20±0.24 mmHg/ml per min) at peak exercise. Conversely no significant changes in exercise capacity and coronary hemodynamics were found following both ID and I. Thus V improves exercise capacity in patients with syndrome X. Benefits may be due to increased myocardial perfusion. The lack of efficacy of other powerful coronary dilators suggests a disregulation of calcium uptake as the most likely mechanism for inappropriate constriction.

Wednesday, March 12, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 4:00PM–5:00PM
Hall D, Georgia World Congress Center
Coronary Artery Disease–Clinical

POST-INFARCTION ANGINA: A HIGH RISK PRESENTATION OF UNSTABLE ANGINA

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The prognostic significance of the clinical presentation was investigated in 559 consecutive patients (pts) undergoing cardiac catheterization during Cardiac Care Unit admission for unstable angina (UA). Fourteen pts had new onset (<6 weeks) effort angina, 91 had new onset (<6 weeks) rest angina, 249 had crescendo angina (acceleration of chronic angina), and 205 had UA within 6 weeks of a documented myocardial infarction (post-MI). Baseline clinical characteristics, results of cardiac catheterization, and follow-up were recorded prospectively. Relationships between baseline characteristics and infarction-free survival from the time of Cardiac Care Unit admission were examined using the Cox regression model.

Left main or 3 vessel coronary disease was found in 21% of new onset effort patients, 26% of new onset rest patients, 38% of crescendo patients and 52% of post-MI patients ($p<.001$). Median LV ejection fraction was 57%, 63%, 60%, and 49% ($p<0.001$), respectively. Infarction-free survival probabilities are given below:

	1 month	6 months	12 months
New onset effort	.88	.73	.73
New onset rest	.92	.87	.83
Crescendo	.91	.91	.89
Post-MI	.81	.78	.69

Infarction-free survival was different for post-MI pts compared to the other groups ($p<.001$). No other significant differences in infarction-free survival were found among groups. Post-MI UA is associated with more severe anatomic disease, worse LV function and worse prognosis than other forms of UA.

PERCUTANEOUS LASER THERMAL ANGIOPLASTY - CLINICAL EXPERIENCE IN PERIPHERAL ARTERY OCCLUSIONS.

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Percutaneous angioplasty is only applicable in a limited number of complete arterial occlusions. To investigate the role of laser-assisted angioplasty, a metal-tipped laser fibre (laser probe) was used to traverse complete arterial occlusions, of length 2 cm to 12 cm, in 12 patients having percutaneous femoral angioplasty, with a mean symptom duration of 22 (range 4-48) months. After initial probing of the proximal limit of the occlusion by a guide wire, 3 lesions were classified as potentially "easy" and 6 probably "difficult" to cross by conventional means. Previous sustained attempts to cross 3 occlusions (6, 9 and 12 cm long) had failed; these were classified as "impossible". The probe was applied using 10 watts Argon laser power for 4 to 20 seconds. There was one technical failure, probably due to a false channel produced by the initial guide wire, without sequelae. All 3 "impossible" occlusions were successfully traversed. In all 11 successes a sufficient channel (mean lumen diameter (MLD) 1.27 ± 0.326 mm (SD)) was produced for subsequent passage of a balloon catheter for definitive dilatation (MLD 2.89± 0.98 mm (SD)). Thus the laser probe can traverse complete arterial occlusions not amenable to conventional angioplasty techniques, and produces an adequate initial channel prior to balloon dilatation. This has implications for widening the role of percutaneous angioplasty.

BALLOON ANGIOPLASTY FOR TOTAL CORONARY OCCLUSION NOT ASSOCIATED WITH EVOLVING MYOCARDIAL INFARCTION

David R. Holmes Jr., M.D., F.A.C.C., Ronald E. Vlietstra, M.D., F.A.C.C., Guy S. Reeder, M.D., F.A.C.C., John F. Bresnahan, M.D., F.A.C.C., Jeffrey M. Piehler, M.D., Mayo Clinic, Rochester, MN.

The role of percutaneous transluminal coronary angioplasty (PTCA) in patients (pts) with total coronary arterial occlusions requires continued evaluation. Through August 1985, PTCA was attempted in 74 pts with total coronary occlusion not associated with evolving acute myocardial infarction (AMI). There were 55 males and 19 females (mean age 58 years). Twenty-five pts had a history of AMI within 1 month prior to PTCA. The occluded vessel was the left anterior descending (LAD) in 41, the right coronary artery (RCA) in 24, and the circumflex (LCX) in 9. The mean duration of occlusion estimated from the time between a prior angiogram with a high grade but subtotal stenosis or from the time of onset of acute symptoms to the time of PTCA was 8.0 weeks. PTCA was successful in 49 pts (66%). PTCA was successful in 66% LAD, 67% RCA, and 67% LCX occlusions. The duration of occlusion had a significant impact: of 26 pts with occlusion estimated to be ≤1 week, PTCA was successful in 22 (85%); of pts with occlusions 1 week to ≤12 weeks, PTCA was successful in 65%. In the 8 pts with occlusions >12 weeks, PTCA was successful in 2 (25%). During follow-up, a subset of 26 pts with successful PTCA underwent angiography; 10 (38%) had restenosis. In 9/10, the artery was patent with a significant stenosis, but not complete reocclusion. In conclusion, PTCA is effective for treatment of recent coronary occlusion without associated AMI. When the occlusion is <1 week old, PTCA is successful in 80%. Restenosis rates in this population appear to be higher than in pts without total occlusion.

DOES AORTOCORONARY VEIN BYPASS SURGERY RESTORE NORMAL CORONARY FLOW RESERVE? Robert F. Wilson, MD, Carl W. White, MD, FACC. CV Center, U of Iowa, Iowa City, IA.
Previous studies employing digital subtraction angiography or Xenon 133 measurements of coronary flow reserve (CFR) have suggested that vein bypass surgery (VBS) does not restore normal CFR. These studies, however, were hampered by methodologic limitations in measuring CFR, and by failure to assess abnormalities in the myocardium perfused by the graft which are known to limit coronary vasodilator capacity [e.g. hypertrophy (LVH) or infarction (MI)]. To further investigate this question, we determined CFR using an extensively validated selective Doppler catheter (DC) in 11 pts. with 20 vein bypass grafts (VBG) leading to nonstenotic distal coronary vessels (10 LAD, 5 Cx, 5 RCA). Twelve VBG perfused normal myocardium (N MYO) and 8 perfused abnormal myocardium (ABN MYO; 3 LVH, 5 prior MI). The DC was positioned in the mid portion of the graft and CFR measured as the peak/resting velocity ratio following selective graft injection of a dose of papaverine previously shown to cause maximal coronary vasodilation. These results were compared to DC measurements of CFR obtained in 13 patients with normal coronary arteries and normal myocardium (N coronary - N MYO) (5 RCA, 4 Cx, 4 LAD).

Results (mean±SEM):	n	CFR	range
N Coronary (N MYO)	13	5.1±0.6	3.7-8.3
VBG (N MYO)	12	5.2±0.4**	3.7-7.6
VBG (ABN MYO)	8	2.4±0.2*	1.8-3.2

* p<0.01 vs. N Coronary (N MYO) or VBG (N MYO)
** p=NS vs. N Coronary (N MYO)
Hence, if the myocardium perfused by the graft is abnormal, then CFR is usually diminished. If the graft perfuses a nonstenotic coronary vessel and normal myocardium, however, the VBS does restore normal CFR.

INTRAVENOUS DIPYRIDAMOLE IN DETECTING CORONARY STENOSIS. ASSESSMENT BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY AND RADIONUCLIDE ANGIOGRAPHY.
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Dipyridamole-induced vasodilation may contribute in identifying patients with coronary artery stenosis (CAD). Thus, in 22 patients with documented coronary artery stenosis by selective coronary arteriography without myocardial infarction (age 55±8), and 21 age matched controls without CAD, two-dimensional echoes were obtained under basal conditions and after dipyridamole (0.75 mg/kg i.v.). Percent ejection fraction (EF) and wall motion score index (WMSI) were calculated. In the same subjects, radionuclide angiography was also performed in different day before and after dipyridamole. In controls, EF measured by two-dimensional echocardiography, rose after dipyridamole from 58±8 to 76±8 ($p < .01$), whereas in CAD patients it decrease from 51±11 to 42±10 ($p < .05$). Similary WMSI in CAD patients decrease from 0.8 and basal conditions, to 0.6 after dipyridamole ($p < .01$). EF measued by radionuclide angiography increased with dipyridamole from 54±15 to 42±12 ($p < .01$) in CAD patients. A close correlation was found between EF changes measured with two-dimensional echocardiography and radionuclide angiography ($r=0.86$, $p < .01$). Thus, in CAD patients dipyridamole reduces EF and WMSI probably by inducing coronary steal; these changes are detectable both by two-dimensional echocardiography and radionuclide angiography.

LASER TREATMENT OF ATHEROSCLEROSIS IN THE MONKEY: REENDOTHELIALIZATION WITHOUT THROMBOSIS EFFECTED BY FIBEROPTIC METAL CAP.
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To study the acute and chronic effects of laser application to atherosclerotic plaques, four 15-year-old monkeys (Macaca Mulata), 5.4 to 9.3 kg, fed an atherogenic diet for 7-8 years were used. Following persantine 50 mg bid for 72 hours, anesthesia was performed with Ketamine 5 mg/kg IM and Isoflurance. Angiography showed moderate to extensive mural plaques in abdominal aorta and iliac arteries. Via a 3.7 mm diameter fiberoptic scope, a metal cautery cap-tipped laser fiber was guided to plaque sites for laser application of energies from 1.5 to 9 joules. No effect was seen at 1.5 to 2 joules applied perpendicularly, but 3 to 6 joules applied tangentially produced superficial burn. Six joules applied perpendicularly produced burn into vasavasorum and 9 joules applied tangentially produced burn into tunica media. Three months post-treatment with 9 joules, the lased area had healed without thinning of the vessel wall. Thromboses of the vessel at site of laser treatment did not occur. These experiments show angle of application of cautery cap influences depth of burn; reendothelialized scar post-laser treatment does not result in aneurysm formation provided burn depth is controlled.

CORONARY FLOW RESERVE LATE AFTER PTCA - DO THE EARLY ALTERATIONS PERSIST? Robert F. Wilson, MD, Philip E. Aylward, MD, Wayne N. Leimbach, MD, Charlotte L. Talman,RN Carl W. White, MD, FACC. CV CTR., U of IA, Iowa City, IA.
We have recently shown that quantitative measurements of coronary artery stenosis (CAS) [percent area stenosis (%AS) and minimum lumenal cross-sectional area (mCSA) measured using Brown/Dodge quantitative coronary angiography (QCA)] correlate highly with measurements of coronary flow reserve (CFR) obtained using a 3 Fr. coronary Doppler catheter (CDC) and maximally vasodilating doses of intracoronary papaverine (P). We have also shown that immediately following successful PTCA, coronary flow reserve remains depressed in some patients and that neither quantitative measurements of lumenal stenosis nor the translesional pressure gradient correlates with CFR. To determine if this dissociation beteween lesion severity and coronary flow reserve persists, we studied 17 patients 5.4±.6 months following PTCA. Angiograms of the dilated vessel were obtained in orthogonal projections and analyzed using QCA. A CDC was placed proximal to the lesion and CFR measured using P. CFR by this technique in normal vessels is >3.7 peak/resting velocity (mean±SEM, 5.1±0.6). In patients with <70 %AS immediately after PTCA, 8/16 had low CFR (<3.5). In contrast, all patients studied late after PTCA or without PTCA had normal CFR if %AS was <70 ($p<0.01$).

Correlation (r value)	CAS-No PTCA (n=24)	PTCA-early (n=19)	PTCA-late (n=17)
%AS vs. CFR	0.82	0.11	0.83
mCSA vs CFR	0.70	0.10	0.72

Hence, in contrast to lesions studied immediately after PTCA, lumen stenosis measured precisely with QCA correlates highly with coronary flow reserve both before and late following PTCA. These results suggest that the dissociation between lesion stenosis and CFR measured immediately after PTCA does not persist.

INHIBITION OF ^{51}Cr-LABELLED PLATELET ACCUMULATION AFTER BALLOON ANGIOPLASTY IN RABBITS: COMPARISON OF HEPARIN, ASPIRIN, AND OGS 13080, A SELECTIVE THROMBOXANE SYNTHETASE INHIBITOR.

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Despite pretreatment with antiplatelet and anticoagulant agents, platelet accumulation (PLT-A) may be responsible for the restenosis which complicates balloon angioplasty (BA). By inhibiting thromboxane A_2 but not prostacyclin production a selective thromboxane synthetase inhibitor, OGS 13080, may be more effective in inhibiting PLT-A after BA. Therefore, ^{51}Cr-platelet accumulation was quantitated 30 minutes after successful BA in a total of 70 significant rabbit iliac stenoses pretreated with the following regimens:

Group	n	PLT x 10^6/cm (x + SD)
Control (Saline IV)	29	44.1 ± 50.4
Heparin (500 U/kg IV)	12	31.6 ± 36.1
Aspirin (10 mg/kg po)	11	125.3 ± 247.2
OGS 13080(1 mg/kg/hr IV)	18	13.9 ± 14.9*

*$p < 0.02$ vs. control

Thus, OGS 13080 significantly reduced PLT-A while heparin and aspirin treatment did not. The variability in neointimal dissection noted on histologic examination accounted for the high standard deviation noted in each group.

In this experimental model, a selective thromboxane synthetase inhibitor is more effective than heparin or aspirin in inhibiting PLT-A after BA. Further studies to evaluate the effectiveness of thromboxane synthetase inhibitors on restenosis are warranted.

THALLIUM-201 SINGLE PHOTON EMISSION TOMOGRAPHY USING ORAL DIPYRIDAMOLE IN THE ASSESSMENT OF CORONARY STENOSIS IN PATIENTS UNDERGOING CORONARY ANGIOPLASTY.

Avanindra Jain, M.D., John J. Mahmarian, M.D., Albert E. Raizner, M.D., F.A.C.C., John M. Lewis, M.D., F.A.C.C., Robert Roberts, M.D., F.A.C.C., Mario S. Verani, M.D., F.A.C.C. The Methodist Hospital, Baylor College of Medicine, Houston, TX.

Objective assessment of the significance of coronary artery stenosis in patients being evaluated for coronary angioplasty (PTCA) by traditional stress testing is hampered by inadequate exercise performance and/or use of cardiac medications. We evaluated oral dipyridamole (300mg) combined with thallium (Tl)-201 single photon emission computerized tomography (SPECT) in 16 patients pre- and 3 days post-PTCA. Cardiac medications were not discontinued. Three mCi of Tl-201 were injected at onset of angina and ischemic ECG changes (4 patients) or 1 hour after dipyridamole (12 patients). Transaxial tomographic images were obtained over an arc of 180° and reoriented in the short axis, horizontal long axis and sagittal axis. Planar images were obtained using standard techniques. Ischemia was present in the areas supplied by the stenosed vessel in 14 patients by tomography and in only 8 patients by planar imaging. PTCA reduced the mean cross-sectional area stenosis from 90% to 35%. All patients but 2 had negative tomographic scans after successful PTCA. SPECT in conjunction with oral dipyridamole demonstrated hemodynamically significant coronary stenosis in larger percentage of patients then planar images (89% vs 50%). Thus, dipyridamole Tl-201 tomography provides a safe and sensitive means of evaluating the hemodynamic significance of coronary stenosis and in PTCA patients it affords early objective documentation of the adequacy of dilatation without requiring exercise or withdrawal of medications.

Rotating Mechanical Angioplasty in Atherosclerotic Iliac Arteries in Rabbits. D. Dennis Hansen, David Auth, Rudy Vracko, James L. Ritchie. Seattle VA Hospital and University of Washington, Seattle, WA.

Percutaneous transluminal coronary angioplasty is unsuccessful in 10% of cases and restenosis occurs in up to 30%. We are studying a new, rotating, ablation tip atherectomy device (AD) capable of opening narrowed atherosclerotic arteries. The AD consists of a .042 inch diameter, rapidly rotating ablative tip with a .005 inch radiopaque central guidewire. The guidewire can be steered independently across a narrowed or obstructed arterial segment. It then serves as a rail over which the rotating, micro dissecting tip of the AD can be safely advanced. We fed 18 rabbits a 2% cholesterol diet for 10 weeks. After the first 14 days of the diet, we disrupted the intima of the right iliac artery by repetitive passes with an inflated Fogarty catheter. Cholesterol levels at this time ranged from 1600 to 3600 mg%. After the final 8 weeks of the diet, contrast angiography was performed. Six rabbits had developed angiographic stenosis, four had greater than 80% narrowing, and 2 had complete occlusion. The guidewire was first passed and was followed by the rotating dissection head. In all cases, angiograms demonstrated a new lumen equal to the size of the rotating device. One perforation was seen in an occluded artery. Histology of the excised arteries demonstrated severe atherosclerosis.

We conclude that a rotating, micro dissection catheter can open narrowed or blocked atherosclerotic arteries in rabbits. This approach provides a direct and easily performed alternative to laser ablation.

TANDEM BALLOON CATHETER FOR CORONARY ANGIOPLASTY.

Bernhard Meier, M.D., Leo Finci, M.D., Giuseppe Steffenino, M.D., Wilhelm Rutishauser, M.D., F.A.C.C., Cardiology Center, University Hospital, Geneva, Switzerland.

The tandem balloon catheter is a triple lumen steerable catheter for coronary angioplasty with 2 seperately inflatable balloons mounted at the tip. The diameter of the distal balloon is smaller than the diameter of the proximal one. Indications and results of 26 consecutive patients (pts) treated with a tandem balloon catheter are reviewed.

The balloon diameters of 24 tandem catheters used were 2.0/3.0 mm. The remaining 2 catheters had diameters of 2.5/3.4 mm. The length of each balloon is 20 mm. Adequate distal pressure measurements were obtained in 71% of the cases. In 10 pts the tandem balloon was chosen because of 2 or more stenoses in different segments of the same coronary artery. Angioplasty was successful for all lesions in 5 pts and for at least the strategic lesions in 5 pts. In 1 pt of the latter group, the tandem balloon catheter had to be replaced by a single balloon catheter to succeed. In 7 pts the tandem balloon was chosen to dilate stenoses in 2 different coronary arteries of disparate calibers. Angioplasty was successful for both vessels in 3 and for 1 vessel in 4 pts. In 6 pts the tandem balloon was chosen for a very tight stenosis and in 3 pts for a total occlusion in the hope that the rigidity of the triple lumen shaft would facilitate the passing of the obstruction and a predilatation with the small balloon would allow for easy passage of the large balloon. In all 6 tight stenoses the procedure was successful. In 1 pt, however, where the tandem balloon catheter had been used after an unsuccessful attempt with a low profile single balloon catheter, myocardial infarction occured within 24 hours after angioplasty suggesting acute vessel occlusion. Of the 3 total occlusions only 1 could be passed and successfully dilated. In 1 of the 2 failures several other balloon catheters were also tried to no avail.

The tandem balloon catheter provides a handy tool for complex coronary angioplasty. It offers comparable ease in manipulation and pressure transmission and may save time, cost, and radiation exposure by avoiding catheter exchanges.

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IS DIASTOLIC PEAK FILLING RATE DURING EXERCISE A SENSITIVE INDEX TO DETECT PATIENTS WITH CORONARY ARTERY DISEASE?
Tomoyuki Murakami, MD, Otto M. Hess, MD, John D. Carroll, MD, Hans P. Krayenbuehl, MD. University Hospital, Zurich, Switzerland

Radionuclide studies have shown that diastolic peak filling rate(PFR) during exercise(Ex) is more sensitive than ejection fraction(EF) to detect patients(pts) with CAD. To evaluate this concept, we used biplane angios and micromanometry and assessed global and regional diastolic filling dynamics at rest(R) and during supine bicycle Ex in 22 pts with CAD and Ex-induced asynergy, and in 10 controls(C). Time-volume curves from biplane angios and time-area curves for 6 regions of the RAO angio were constructed. Normal limits of regional EF(REF) were determined from C. Of 132 regions in CAD 26 were normokinetic at R and during Ex, with an increase in REF during Ex(non-ischemic regions:nIR) and 54 were normokinetic at R but hypokinetic during Ex(ischemic regions:IR). Global EF(%), global PFR(GPFR;ml/s), regional PFR(RPFR;cm^2/s), the early diastolic area increase from mitral valve opening(MVO) to the lowest pressure(P)(Ae;cm^2), and P at MVO(MVOP;mmHg) were determined.

	C	CAD		nIR(n=26)	IR(n=54)
EF(R/Ex)	63/67*	62/50*§	RPFR(R/Ex)	23/37*	26/23*
GPFR	565/928*	631/891*	Ae	1.2/1.8*	1.2/0.8*

* P<.05 vs R; § P<.05 vs C

During Ex, MVOP increased from 17 to 39 mmHg(P<.05) in CAD. Of 26 nIR, RPFR increased in 25(96%) regions and Ae increased in 24(92%) regions during Ex. Of 54 IR, RPFR also increased in 23(43%) regions and Ae increased in 17(31%) regions during Ex. Reflecting regional filling dynamics, GPFR increased in 21(95%) CAD pts during Ex, although EF decreased in all pts. During Ex, GPFR increases in CAD as in C, due to an increased driving P(↑MVOP). Thus, GPFR is not a sensitive index for detecting pts with CAD.

CORONARY VASOMOTOR RESPONSE TO ISOMETRIC EXERCISE IN PATIENTS WITH AND WITHOUT SIGNIFICANT CORONARY ARTERY STENOSES.
Rodney L. Henry, MD, John T. Miller, MD, Morton J. Kern, MD, FACC and Robert A. O'Rourke, MD, FACC. University of Texas Health Science Center and VA Hospital San Antonio, TX.

A recent study reported constriction of epicardial stenoses in response to isometric handgrip (HG) exercise with an estimated 243% increase(↑) in angiographic stenotic flow resistance (R). To examine the effect of this response on directly measured coronary R, we studied 19 patients (pts) by measuring total coronary sinus flow(CSF) and great vein flow (GVF) at control (C), during HG, during intracoronary nitroglycerin (ICNTG), and during HG + ICNTG. 9 pts had no significant left anterior descending (LAD) stenosis (gr 1) and 10 pts had >70% LAD stenosis (gr 2). C-CSF averaged 104±5 ml/min, C-GVF 66±4, C-MAP 98±3 mmHg and C-HR 62±2 with no difference between groups. Peak responses vs C are as follows: *p<.05 vs C,± = 1SE

Intervention		%ΔCSF	%ΔGVF	%ΔCSR	%ΔGVR	%ΔMAP	%ΔHR
HG	Gr 1	+14±13	+19±7	+10±14	+6±7	+15±2*	+10±2*
	Gr 2	+13±7	+17±8	+11±7	+6±6	+20±3*	+11±2*
NTG	Gr 1	+74±13*	+72±1*	-43±3*	-42±4*	-2±2	+2±1
	Gr 2	+53±8*	+35±5*	-35±4*	-28±2*	-5±2	+1±1
HG+	Gr 1	+59±16*	+72±7*	-24±7*	-33±4*	+12±2*	+11±2*
NTG	Gr 2	+76±11*	+60±11*	-32±5*	-25±6*	+16±3*	+11±2*

Both groups had a small ↑ in CSF, GVF, CSR, and GVR, and a significant ↑ in mean arterial pressure (MAP) and HR with HG. HG did not change the CSF or CSR response to ICNTG in either group. The GVF and GVR response to ICNTG was unchanged by HG for gr 1. Gr 2 had a greater ↑ in GVF with ICNTG+HG compared to C due to ↑ MAP with HG and no change in the GVR response. We conclude: 1. HG causes an insignificant ↑ in measured CSR and GVR; with no greater ↑ in GVR in pts with LAD stenoses. 2. HG does not blunt the hyperemic response to ICNTG in pts with or without CAD.

UNDERUTILIZATION OF CLINICAL DATA LEADS TO OVERUTILIZATION OF TECHNOLOGY.
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At our hospitals, clinicians use nuclear exercise tests to evaluate virtually all pts with suspected or proven coronary disease (CAD). Since the proper selection of noninvasive tests is critically dependent on the pts likelihood for CAD, which in turn is dependent on the history for angina we prospectively asked all physicians (MDs) who referred out-pts for nuclear exercise tests about their pts angina history. We also asked if they thought their pts had CAD & whether they were treating for CAD. Their pts were then interviewed by project cardiologists who obtained the history for angina using Coronary Artery Surgery Study guidelines. This history was used with pt age & gender to create categories of CAD likelihood: GP I, CAD likelihood <11%;GP II, CAD likelihood >10% <91%; GP III, CAD likelihood >90%. Pts with prior MI, N=66, or CAD at angiography, N=42, are GP IV. MD diagnoses & plans for GPS I-IV are shown.

MD RESPONSE	GP I	GP II	GP III	GP IV
N	58	156	56	108
DEFINITE ANGINA	2%	15%†	18%†	21%†
CAD PRESENT	45%	53%	45%	98%*
ANTIANGINAL RX	50%	67%	69%	79%**
PLAN ANGIOGRAPHY	33%	37%	41%	68%*

* p<.001, ** p<.05 vs GPS I-III. † = p<.025 vs GP I.

MD rarely thought that their pts had definite angina (especially GP I pts), but still diagnosed CAD & treated as if CAD was present. Further, both MD diagnosis of CAD and RX were independent of the pretest likelihood for CAD, differing only for pts with proven disease. Thus MD decision making is not explained by the history they elicit for angina, nor by disease likelihood based on a standardized history, gender & age. It appears that clinical data are underutilized, leading to the overutilization of therapy & testing procedures.

VARIABILITY OF RESULTS DURING REPEAT EXERCISE TESTING IN STABLE EFFORT ANGINA PECTORIS: A CLUE TO THE PRESENCE OF DYNAMIC CORONARY STENOSES.
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Patients (pts) with stable effort angina (EA) often report a history of variable effort tolerance. This study was aimed at assessing whether dynamic coronary stenoses(DCS) can account for a variable exercise capacity. 20 pts with EA and coronary heart disease (CAD) were studied. In 10 of these pts (Group A) the possibility of developing DCS was indicated by a positive result of ergonovine testing (>0.1 mV ST depression and angina) not preceded by obvious increases of heart rate-blood pressure product (RPP). In 4 pts of this group who underwent ergonovine testing also during angiography, ergonovine caused an increase of the severity of coronary stenoses followed by diagnostic ischemic ECG changes and angina. The remaining 10 pts (Group B) who had similar symptoms and severity of CAD but a negative result of ergonovine testing (neither ST shifts nor angina) were used as control group. All pts underwent 2 upright symptom-limited treadmill exercise tests in the morning on different days during 12-lead ECG and blood pressure (cuff) monitoring; the interval between the 2 tests never exceded 2 weeks. In each pt group for each exercise parameter, variability was calculated as mean ± 1SD of the absolute differences between the values during the 2-paired tests. Variability of heart rate and RPP at 0.1 mV ST depression and variability of RPP at onset of angina were significantly higher in Group A than in Group B (12 ± 4 vs 4 ± 4 bpm $p < 0.001$, 3,360 ± 1,900 vs 930 ± 960 bpmxmmHg $p < 0.005$ and 3,880 ± 2,400 vs 1,420 ±1,800 bpmxmmHg $p < 0.04$,respectively). Variability of time to 0.1 mV ST depression, onset of angina and peak exercise was higher in Group A than in Group B, but this difference did not achieve statistical significance. Thus, the variability of results during repeat exercise testing, is higher in those pts with stable effort angina who develop DCS in response to ergonovine testing. In these pts DCS seem to modulate the response to exercise and could account for a history of variable effort tolerance.

LOW-DOSE ORAL DIPYRIDAMOLE PRODUCES CORONARY BLOOD FLOW REDISTRIBUTION ON THALLIUM-201 MYOCARDIAL IMAGING IN PATIENTS WITH CORONARY ARTERY DISEASE.

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University of British Columbia and Vancouver General Hospital, Vancouver, B.C. Canada.

It has been found that IV (0.56mg/kg) and a large oral dose (300mg) of Dipyridamole (D) produce myocardial perfusion abnormalities on Thallium-201 myocardial imaging in patients (pts) with myocardial ischemia. To see if low-dose (100mg) oral D also induced redistribution of coronary blood flow on Dipyridamole/Thallium (D/T) myocardial imaging we studied 8 pts (6 males, 2 females, mean age 63 years) who previously had transient defects (TD) +/- persistent defects (PD) on IV D/T myocardial imaging. Each pt received 100mg of pulverized tablets in 30ml of sugar-free solution. Vital signs and EKG were monitored by a cardiologist. 45 minutes later, 2 mCi of Tl-201 were given IV and serial Thallium imaging began within 5 minutes. Myocardial regional perfusion was assessed by 2 independent observers using original analog images with segmental profile analysis.
8 pts had TD on initial IV D/T myocardial imaging. In 5/8 pts (63%) TD was also present after oral 100mg D. In 3 pts who had TD and PD on initial IV D/T imaging only a PD could be demonstrated after oral 100mg D. One pt with angiographically documented severe triple-vessel coronary artery disease developed chest pain and ischemic EKG changes after the oral dose. No other side effects were seen. We conclude that low dose (100mg) oral Dipyridamole can produce myocardial blood flow redistribution in ischemic areas. This effect may be of clinical significance in patients with coronary artery disease who are on oral Dipyridamole for its anti-platelet effects.

TRANSIENT MYOCARDIAL DYSFUNCTION AFTER DIPYRIDAMOLE INFUSION AN INDEX OF REGIONALLY REDUCED CORONARY RESERVE.

Eugenio Picano MD, Ignazio Simonetti MD, Michele Masini MD, Fabio Lattanzi MD, Mario Marzilli MD, Alessandro Distante MD, Antonio L'Abbate MD FACC. C.N.R., Clinical Physiology Institute, University of Pisa, ITALY.

Aim of this study was to test the hypothesis whether the mechanical behaviour of the LV after dipyridamole (DIP) reflects better the physiological consequences of the coronary stenosis rather than its angiographic severity. In 19 patients with severe (80-99%) proximal isolated stenosis of Left Anterior Descending Artery (LAD) and in 10 controls, regional coronary reserve was evaluated measuring coronary sinus blood flow (CF) after DIP infusion (0.56 mg/Kg in 4 minutes) by positioning into the great cardiac vein the distal thermistor of a 3 thermistor thermodilution catheter, regional contractility was evaluated by means of continuous 2-D echo monitoring. According to the result of the echo monitoring, following DIP the 19 patients were divided in 2 groups IA) with transient regional asynergy in the LAD territory (anteroseptal wall and/or apex), IB) without regional asynergy. No one of the controls (group II) showed regional asynergy. No significant difference was present in the angiographic severity - evaluated by quantitative analysis and expressed as % lumen reduction - of the LAD stenosis between groups IA and IB (89.9 ± 6.3% vs 88.1 ±7.0%). The increase of anterior CF in group IB (136 ± 45%, mean + SD) was similar to group II (166 ± 68%, p = ns), but it was significantly lower in group IA (46 ± 29%, p < 0.01 vs group IB and II). In conclusion, the mechanical behaviour of the LV after DIP reflects better the physiological consequences of the stenosis than its angiographic severity.

THE EXTENT AND RATE OF RAPID CHANGES IN LEFT VENTRICULAR FUNCTION ON EXERCISE AS A PREDICTOR OF CORONARY ANATOMY.

John L. Caplin, M.B., Duncan S. Dymond, M.D., F.A.C.C., James C. O'Keefe, M.B., William D. Flatman, M.Sc. and Roworth A.J. Spurrell, M.D., F.A.C.C., St. Bartholomew's Hospital, London, ENGLAND.

Gold-195m (t1/2=30.5 sec) allows rapid sequential first-pass studies of LV function. Serial imaging was performed in 25 patients (pts), 7 with normal coronaries (nls), 11 with 1/2 vessel disease (VD), and 7 with 3VD, at rest, and at 3 mins, 6 mins, peak, immediately post and 2 mins post exercise (ex). Nls increased their ejection fraction (EF) throughout ex and at 2 mins post-ex EF, 68±6%, was above rest, 60±6% (p<0.05). In 1/2VD pts EF fell during ex. with a maximum fall at peak, 58±10% vs 47±10% (p<0.05), but at 2 mins post-ex EF rebounded above rest value. In 3VD pts EF again fell during ex with a maximum fall at peak, 57±11% vs 35±8% (p<0.001), but no rebound occured. Rates of change in EF related to ex duration and change in heart rate showed significant differences between the groups, but there was considerable overlap:

	nls	1/2VD	3VD
ΔEF/ex dur(%/min)	.6±1.0	-2.1±1.8*	-4.8±2.9*
ΔEF/ Δ HR(%/bpm)	.01±.07	-.19±.16*	-.41±.29*

(*=p<0.01 vs nls)

In conclusion the extent and rate of change in LV function derived from rapid, sequential first-pass studies 1) can differentiate pts with severe coronary artery disease, 2) suggests that there is an overlap in extent of myocardium at risk between pts with and without 3VD, and 3) suggests that an algorithm incorporating ex duration and change in heart rate into the interpretation of EF change may improve the stratification of pts in terms of myocardium at risk.

THE ERGOMETRINE TEST : A PROVOCATIVE TEST FOR CORONARY ARTERY SPASM OR ESOPHAGEAL MOTILITY DISORDERS ?

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Ergometrine (ergo) can evoke coronary spasm in patients with variant angina. The cause of ergo induced chest pain (CP) in the absence of coronary spasm is not clear. To determine whether ergo produced esophageal dysfunction and CP, we evaluated 28 patients by esophageal manometry (EM). Six had CP in response to ergo during cardiac catheterization (group I) and 22 did not (group II). Results of cardiac catheterizations were normal in all patients. EM was performed before and after ergo (0,4 mg I.V.). Results : ergo provocation during EM caused signifiant deterioration in esophageal motility associated with familiar pain in 5/6 group I patients. The motility disorders were characterized by the presence of repetitive contractions of exceedingly high amplitude and long duration in the distal esophagus. There were no ECG changes during any episodes of CP. No patient from group II experienced CP after ergo and only 2/22 developed long duration contractions. Baseline manometry failed to predict a positive response to ergo. Conclusion : in patients with normal coronary angiogram, ergo induced CP without associated coronary artery spasm suggests that esophageal motility disorders originate CP.

CORRELATION OF MINIMUM LUMEN DIAMETER WITH LEFT VENTRICULAR FUNCTIONAL IMPAIRMENT DURING ATRIAL PACING
Jonathan Tobis, MD, FACC, David Sato, MD, Warren D. Johnston, MD, Tim Reese, Orhan Nalcioglu, PhD, Walter L. Henry, MD, FACC

The quantitative analysis of coronary artery disease using percent stenosis is a relative standard that is dependent upon the width of the "normal" segment. Absolute lumen diameter is a less subjective measurement but is usually tedious to obtain. The purpose of this study was to relate measurements of lesion severity to segmental wall motion abnormalities induced during atrial pacing. On line digital acquisition of coronary angiograms were performed in 18 patients to permit rapid access of computer algorithms for quantitative analysis. Low dose (15ml) contrast digital left ventriculograms were obtained at rest and peak pacing. Percent stenosis and absolute minimum lumen diameter were calculated by edge detection methods. These measurements were compared to the functional impairment in global ejection fraction (EF) and segmental percent radial shortening induced during atrial pacing studies. The mean percent stenosis was 63 ± 16% and the mean minimum lumen diameter was 1.3 ± 0.6 mm. The mean EF at rest was 62 ± 16% and at peak pacing was 54 ± 22%. The mean percent radial shortening was 57 ± 24% at rest and at peak pacing was 49 ± 31%. The absolute stenotic lumen diameter correlated most closely with the change in segmental wall motion (r=0.84) compared to the change in global EF (r=0.64). Percent stenosis was also correlated with EF (r=-0.62) and wall motion (r=-0.68). A proximal coronary diameter of <1.4mm tended to identify patients with marked segmental wall motion defects induced by atrial pacing. Thus, absolute minimum lumen diameter corresponds more closely with functional assessments of coronary lesions than do calculations of percent stenosis.

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ENCHANCED REGIONAL LEFT VENTRICULAR FUNCTION AFTER DISTANT CORONARY BYPASS VIA IMPROVED COLLATERAL FLOW
Vasken Dilsizian, MD, Robert O. Bonow, MD, FACC, Cynthia M. Tracy, MD, Richard O. Cannon, MD, FACC, Charles L. McIntosh, MD, FACC, Michael Jones, MD, Dino F. Vitale, MD, Stephen L. Bacharach, PhD and Michael V. Green, MS, NHLBI, Bethesda, Md.

To determine whether coronary artery bypass (CABG) can, through collaterals, improve function in left ventricular (LV) regions not revascularized (because of non-bypassable arteries or occluded grafts), we studied 21 pts with multivessel coronary artery disease (CAD) by radionuclide angiography and coronary arteriography before and 6 mos after CABG. All had proximal stenosis of the left circumflex artery (LCX) or a major obtuse marginal branch. Pts were exercised after all cardiac medicines were withdrawn. LV regional function was assessed by dividing the LV region of interest into 20 sectors; the 8 sectors corresponding to the posterolateral free wall were used to assess function in the LCX distribution. For the total group, CABG significantly increased both the global LV ejection fraction (EF) during exercise (40±13 to 51±14%, p<.001) and the magnitude of change in EF from rest to exercise (-8±10 to +2±6%, p<.001). Such improvement was observed in 8/10 pts with all stenoses bypassed, but also to an equivalent degree in 9/11 pts in whom the LCX was not bypassed. In 10 of these 11 pts, exercise induced wall motion abnormalities improved and regional EF during exercise increased (from 49±15 to 65±16%, p<.001) in the lateral wall that was not revascularized. Improved collateral perfusion to this region was demonstrated angiographically in 8/10 pts. Hence, many pts with a non-bypassable coronary artery may still benefit from CABG, if the jeopardized myocardium is perfused by collateral vessels supplied by a stenosed artery amenable to bypass surgery.

LAD LESION MORPHOLOGY AS A PREDICTOR OF ANTERIOR INFARCTION IN CASS
Stephen G. Ellis, M.D., Kevin Cain, Ph.D., Lloyd Fisher, Ph.D., Martial G. Bourassa, M.D., F.A.C.C., Edwin L. Alderman, M.D., F.A.C.C. Stanford University, Stanford, California and CASS Investigators.

Trials assessing the benefits of coronary revascularization have assumed that risk of MI is determined primarily by the degree of coronary stenosis (%CS). We examined the extent to which 21 aspects of LAD stenosis morphology contributed to the risk of anterior MI (AMI) in CASS. AMI occurred within 3 years after baseline angio in 5% of 4,598 medically treated patients (pts) with ≥30% LAD stenosis. 118 of the AMI pts had good quality angios which were compared against angios from 141 non-AMI pts, matched on the basis of %CS in the LAD and presence of disease in other vessels. Morphology was assessed in 557 LAD lesions by an experienced angiographer unaware of clinical outcome. Predictive strength was expressed for each parameter as the odds ratio (R) for AMI.

Univariate analysis revealed luminal irregularity; i.e., edge roughness (R=4.5; p=.001), stenosis length (R=1.7; p<.01), lesion assymmetry (R=1.9; p=.06) and jeopardized collaterals (R=2.7; p=.08) to be risk factors for AMI. Parameters such as vessel angulation at lesion site, lesion involving a bifurcation, acuity of proximal lesion edge, tandem lesions and distal stenoses were not predictive. Multivariate analysis which included clinical and LAD lesion morphology variables as well as %CS ranked lesion roughness, %CS, smoking and male sex in that order to be predictive of AMI.

The fact that luminal irregularity increases the risk of AMI from a given stenosis by four-fold may relate to lesion potential for thrombogenesis. This was suggested by the fact that the statistical power of roughness declined with the interval from baseline angio. We conclude that morphology should be considered in future angio-based clinical trials and may be an important factor in making decisions about revascularization.

SURVIVAL ANALYSIS OF MEDICAL AND PROMPT SURGICAL THERAPY IN PATIENTS WITH TRIPLE VESSEL CORONARY ARTERY DISEASE AND SEVERE ANGINA PECTORIS: A CASS REGISTRY STUDY.
William O. Myers, M.D., F.A.C.C., Bernard J. Gersh, M.D., F.A.C.C., Lloyd D. Fisher, Ph.D., F.A.C.C., Michael B. Mock, M.D., F.A.C.C., David R. Holmes, M.D., F.A.C.C., Hartzell V. Schaff, M.D., F.A.C.C., M. McConney, Ph.D., Thomas J. Ryan, M.D., F.A.C.C., George C. Kaiser, M.D., F.A.C.C., Robert L. Frye, M.D., F.A.C.C. and CASS Investigators, Marshfield, Clinic, Marshfield, WI.

Results of coronary artery bypass surgery were evaluated in 2600 non-randomized patients with 3 vessel disease (3VD) in angina class III-IV, 679 treated medically and 1921 treated surgically within the time from entry in which 95% of those who received surgery at each CASS site did so, about 90 days. Six-year survival was 55% with medical and 83% with surgical therapy (p < .0001). With normal LV wall motion (CASS score 5) and with 0 or 1 proximal vessels stenosed (PROXVES) significantly longer survival with surgery in 3VD was not found. With 2 and 3 PROXVES there was survival benefit for surgery with normal LV. With increasing LV dysfunction (score 6-9, 10-15 and 16-30), and 1 to 3 PROXVES, benefit increased.

Cox analysis identified variables predicting survival; surgery had an independent effect for survival. Analysis by propensity score (PROSCOR) identified variables which influenced therapy received. Divided into quintiles of the PROSCOR, groups with equal likelihood of surgery (1:10 to 1:1) were compared. Survival benefit was found in all quintiles of PROSCOR. Relative survival benefit of surgery increased with decreasing propensity for operation. Conclusion: relative survival benefit of surgery in 3VD and severe angina increases with increasing anatomical severity (above 1 PROXVES in normal LV) and decreasing likelihood of operation.

AORTO-CORONARY BYPASS SURGERY IN PATIENTS WITH A SEVERELY COMPROMISED LEFT VENTRICLE.

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Consecutive patients (pts) (284) on one cardiology section whose ejection fraction (EF) was 35% or less by radionuclide angiography underwent aorto-coronary bypass (ACB) alone (179) and/or LV aneurysm repair (LVA) (105) between 1977-1983. Class III-IV angina was present in 76 and 65% and major LV failure in 40 and 56% of pts in these two groups respectively. Mean ischemic and pump time were 31 and 58 min in ACB and 38 and 62 min in LVA, with average number of grafts, 3.6 and 2.2, respectively. Early and late prognosis was studied. Postoperative interventions: intraortic balloon, pressors, resuscitation, were required in 4, 14 & 6% of ACB and 10, 25 & 11% of LVA pts. Perioperative myocardial infarction occurred in 10.6% (30/284). Cerebral complications occurred in 0.6% (1/179) of ACB and 5.7% (6/105) of LVA pts. Early death occurred in 3.4% (6/179) of ACB and 8.6% (9/105) of LVA pts.

Follow-up (1-95, av 30 months), was available on 253 (89%) pts. No limiting symptoms were present in 189 (85%) survivors. Ejection fraction improved 6-10% points in 22% (59/269) and more than 10% points in 29% (78/269) pts. Return to work was reported in 61% (135/222) of survivors. Late death occurred in 31 pts. Actuarial survival (5 yr.) was 72%, 89% and 80% amongst pts. with preop EF less than 20% (135), 20-35% (149) and total group (284).

We conclude that patients with major LV dysfunction have acceptable early mortality. The longterm symptom relief and survival is excellent.

INFLUENCE OF OPERATIVE THERAPY ON LONG-TERM PROGNOSIS IN PATIENTS WITH THREE-VESSEL CORONARY ARTERY DISEASE

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Controversy persists regarding timing of surgical therapy in symptomatic patients with angina and three-vessel coronary artery disease (3VD). Of 2125 3VD patients diagnosed at catheterization since 1969 by 75% stenosis criteria (left main and emergency surgery patients excluded), 1060 received medical therapy and 1065 underwent surgery. 937 patients having early surgery (ES), i.e. within 60 days of catheterization, were compared to the remaining 1188 medical and late surgery (M+LS) patients to examine factors influencing outcome. There were 141 total cardiovascular deaths in ES and 382 in M+LS. Baseline differences included mean ejection fraction, .53 in ES vs .46 in M+LS ($p<.01$), and progressive or pre-infarctional angina 68% vs 49% ($p<.01$). After adjusting for these and other baseline variables as well as the bias due to ES waiting time with the Cox proportional hazards model, ES showed improved survival compared to M+LS ($p<.01$). The adjusted 5 year survival was 90% after ES and 76% with M+LS. The relative treatment benefit was the same for all levels of medical risk, with the absolute magnitude of improvement in survival being greater in the higher risk patients. Thus, ES improves survival in symptomatic patients with 3VD. The clinical importance of ES is related to the underlying medical prognosis and is greatest in patients at increased medical risk, such as those with worse symptoms or reduced ejection fraction.

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Author Present: 3:00PM–4:00PM
Hall D, Georgia World Congress Center
Myocardial Infarction—Clinical

SUBENDOCARDIAL SPARING IN MYOCARDIAL INFARCTS OF PATIENTS WITH AND WITHOUT VENTRICULAR TACHYCARDIA.

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The ability of endocardial resection to halt ventricular tachycardia (VT) indicates the possible importance of subendocardial sparing (SES) of myofibers for the maintenance of VT. To see how SES differs in patients with and without VT, the hearts were examined from 22 deceased patients with sustained VT and 21 patients without VT who had an old or organizing myocardial infarct (MI). Circumferential histologic sections were made from a cross section of the LV that included a representative region of the MI. SES was defined as all viable myofibers between the LV cavity and a solid MI scar. The dimensions of SES were measured. The amount of patchy SES fibrosis was estimated, and hydropic change (myocytolysis) was judged using a semi-quantitative scale of 0 to 4+. The mean circumferential extent of SES around the LV cross section was greater in the VT than the non VT group (161 vs. 76mm, $P<0.0005$), however, mean SES thickness through the LV wall was not different (0.71 vs. 0.76mm, $p=0.64$). The mean degree of hydropic change was significantly greater for the VT than the non VT group (1.4 vs. 0.3, $p< 0.001$), but the mean fibrosis was not (14% vs 13%, $p=0.46$). Thus, patients with VT have more SES. Interestingly, the SES in the VT group does not have more patchy fibrosis, even though patchy fibrosis is thought to lead to fractionated activation and VT. However, the VT group does have more hydropic change suggesting increased chronic ischemia in the VT group.

CAN ION CHANNELS BE ANTIGENS TO IMMUNOGLOBULIN G (IgG) IN MYOCARDIAL INFARCTS? M. Rappaport, H. Hammerman, M.D., H. Meiri, Ph.D., The Rappaport Institute and School of Medicine, Technion, Haifa, Israel.

Radioimmunoassay showed a high level of free IgG in patient sera within the first 24 hours following first (3.4 ±1.9 mg/ml) ($\bar{X}$±SD) and recurrent (3.4±1.1 mg/ml) myocardial infarction (MI). IgG level after MI remained high at 4 and 8-10 days. Sera of subjects without cardiovascular disease contained 20±2.3 ug/ml only. Four ion channel specific monoclonal antibodies (mAb) were then used to investigate the possibility that their antigens also might induce an elevation of IgG in patient sera. Our mAb's were: 1) 72-14 that depresses $\dot{V}_{max}$ in canine Purkinje fibers by modulating fast Na^+ channel conductance, 2) 61-44 that binds to Na channel molecule without physiological activity, 3) 72-38 that competitively blocks the binding of tityus γ toxin to the activation gate of fast Na channel and 4) 79-17 that modifies both Na channel and Ca^{2+} dependent K^+ channel. A 50±9% reduction ($p<0.001$) of 72-14 binding and a 50±23% reduction ($p<0.01$) of 61-44 binding were found in presence of sera of patients 24 hours after first MI. After recurrent MI the binding of 72-14 and 61-44 was further depressed (94±7, $p<0.001$, and 57±9, $p<0.002$ respectively). Suppression of binding persisted when the same patient sera employed at 4 and 8-10 days after first and second MI's. The binding of 72-38 and 79-17 was modified insignificantly. Sera of subjects without cardiovascular disease modified binding of each mAb by no more than 7-12%. The correlation between sera level of free IgG and their ability to modify mAb binding to their channel antigen was improved from first to recurrent MI. We conclude that some ion channel determinants may be modified prior to first but more significantly prior to recurrent MI and may induce IgG production in patients.

HEMODYNAMICALLY IMPORTANT RIGHT VENTRICULAR MYOCARDIAL INFARCTION: ACUTE AND 1 YEAR MORTALITY AND IDENTIFICATION OF HIGH RISK PATIENTS.

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No study has systematically evaluated consecutive patients (pts) with hemodynamically important RV myocardial infarction (MI) in a prospective fashion to determine acute and one year (yr) mortality as well as what factors identify a high risk subgroup of RVMI pts. We evaluated clinical, hemodynamic and ECG variables in 27 consecutive pts who met the RVMI criteria of both a RA pressure (P) ≥10mmHg and a RA:pulmonary artery wedge P ≥0.8. Three pts died within the first 72 hours, Group 1, and 24 survived hospitalization, Group 2. There were no clinical variables that separated Groups 1 & 2. All Group 1 pts had a stroke volume index (SVI) <20ml/m^2, LV stroke work index (SWI) ≤20g•m/m^2, and summed ST depression V_1-V_4 >10mm, while no Group 2 pts demonstrated either of these hemodynamic and ECG findings. Two Group 1 pts at autopsy had extensive RVMI and LVMI involving LV postero-lateral and anterior walls; while the remaining Group 1 pt had cardiomegaly and pulmonary edema on chest x-ray. Group 2 pts had mean radionuclide angiographic (RNA) RV ejection fraction (EF) 0.29±0.07 with evidence of akinesis or dyskinesis on wall motion analysis and a mean LVEF of 0.56±0.11. At 1 yr follow-up only 1 pt died due to anterior MI. We conclude that RVMI which is confirmed by both hemodynamic monitoring and RNA has a low acute and 1 yr mortality when extensive LVMI is not present. Also, the combination of SVI <20ml/m^2, LVSWI<20 g•m/m^2, and summed ST depression V_1-V_4 >10mm portends a poor prognosis in acute RVMI due to extensive concomitant LVMI.

RECURRENT CHEST PAIN IN PATIENTS WITH PRIOR MYOCARDIAL INFARCTION: HIGH FREQUENCY OF RESIDUAL JEOPARDIZED VIABLE MYOCARDIUM IN AREA OF PREVIOUS INFARCTION.

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We examined the location of myocardium at risk in patients with prior myocardial infarction (MI) who present with chest pain. A series of 61 consecutive patients with a prior (1 mo-8 yr) Q-wave MI who had stress Tl-201 imaging and cardiac catheterization were examined. Regional Tl-201 defects and the presence of Tl-201 redistribution, a marker of ischemic viable myocardium, were compared to corresponding myocardial segments with MI based on analysis of EKG Q-waves.

In 59 (98%) patients, Tl-201 perfusion defects were present in the area of prior MI. Tl-201 redistribution was present in 1 or more of these segments in 33 (54%) patients. Among 32 patients with multivessel disease, Tl-201 defects outside the MI were present in 16, including 13 with redistribution. A total of 38 patients had redistribution: in 25 (67%) this was limited to the area of MI; in only 5 (13%) was redistribution limited to outside the MI. The influence of clinical, exercise, and coronary variables on the presence of Tl-201 redistribution within the area of prior MI was examined using multiple logistic repression. Significant positive correlates of infarct redistribution were: 1) the presence of good collateralization of the distal coronary artery supplying the MI ($p<0.05$), and 2) the time since the prior MI ($p<0.05$).

In conclusion, there is a high frequency of residual jeopardized viable myocardium within the area of MI among patients with prior MI and recurrent chest pain. The presence of this persistent myocardium at risk appears to be related to: 1) collateralization of vessels supplying the area of MI, and 2) the duration of time since the MI.

THE ELECTROCARDIOGRAPHIC ESTIMATION OF VENTRICULAR IMPAIRMENT (INFARCTION SIZE?) IN ACUTE INFERIOR MYOCARDIAL INFARCTION

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Numerous studies supporting electrocardiographic (ECG) estimates of inferior (inf) infarction (MI) extent have been reported. However, a multivariate discriminant instrument for estimating acute inf MI size at this institution rejected precordial ST segment shifts as a predictive variable. Therefore, a new ECG score employing QR data and ST segment shifts in lead I, II, III and aVf combined with depth and distribution (lead number) of precordial ST depression was employed to analyze the first (emergency room) ECG of 45 consecutive inf MI patients preceding contrast ventriculography within six hours of chest pain onset. A score of "1" reflected the most extensive QRST changes in the greatest number of leads, and "4", the least. These scores were related to the extent of acute ischemia/MI per ejection fraction (EF) as follows (mean ± SEM):

score	n	EF
1	12	.52±.03
2	16	.51±.02
3	14	.51±.02
4	3	.44±.03
p (ANOVA)		NS

CONCLUSIONS: Estimation of the extent of acute inf ischemia/MI by ECG within six hours of chest pain is highly inaccurate and therefore not helpful in theraputic decision making.

PROGNOSTIC SIGNIFICANCE OF TYPE AND LOCATION OF MYOCARDIAL INFARCTION.

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The prognostic significance of non Q-wave (NQ) vs Q-wave (Q) myocardial infarctions (MI), and of anterior (ant) vs inferior (inf) MIs was evaluated in 625 patients (pts) with a first MI. Those with NQMI (190 pts) had more diabetes (20.5% vs 13.6%, $p < 0.03$), and were more likely to be female (38% vs 23%, $p < 0.01$) than those with QMI (435 pts). All other risk factors were similar.

(N =)	NQMI (190)	QMI (435)	p
Infarct Size Index (ISI) (CK-MB ISI, g•eq/m^2)	12.8	20.9	< 0.0001
Ejection Fraction on admission (EF,%)	50.9	45.8	< 0.0004
In-hospital CHF (%)	23.2	30.6	0.06
Recurrent MI (4 yr,%)	17	10	< 0.01
Cardiac Death (4 yr, %)	17	20	NS

Compared to QMI pts, those with NQMI had a smaller ISI and a higher EF on entry, yet had more recurrent MIs and a similar 4 year cardiac mortality.

When pts were divided into ant (316 pts) and inf (309 pts) MI locations, however, pts with ant MI had a higher 4 yr mortality than pts with inf MI (28% vs 14%, $p < 0.0001$) regardless of QMI or NQMI type, or ISI.

We conclude that although type of MI (QMI vs NQMI) and infarct size influence prognosis, location of MI (ant vs inf) is a more important determinant.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

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From 11/81 to 5/85 50 patients (38 male, 12 female) had percutaneous transluminal coronary angioplasty (PTCA) performed in the setting of acute myocardial infarction (AMI). Mean age was 54±11 years. Infarct-related vessel was the LAD in 27 (54%), RCA in 20 (40%), and circumflex in 3 (6%). 38 pts (76%) had initial total occlusion (TO). PTCA alone was used successfully as the primary approach in pts with subtotal occlusion (12 pts) and those with TO and angiographic evidence of an antegrade channel (6 pts). There were no acute complications in this subgroup. Intra-coronary thrombolytic therapy (TT) was attempted in 32 pts with TO and thrombosis. Of these, reperfusion with TT alone was achieved in 23 pts (72%). PTCA was then successful in relieving the stenosis in 20/23 pts (87%) with successful TT and in 6/9 pts (66%) with unsuccessful TT. PTCA failure occurred in 6 pts due to inability to cross in 1 and thrombus resistant to numerous inflations in 5. Four of these proceeded to emergency surgery (CABG). Five others had CABG within 24 hrs because of diffuse disease in 3 and acute closure syndrome in 2. There were two in-hospital cardiac deaths (septal rupture on day 8 after PTCA; sudden death on day 9).

Conclusion: PTCA may be ideal for patients with AMI without coronary thrombus. In pts with coronary thrombosis, the combined use of PTCA and TT may be associated with relative low risk of acute coronary reclosure.

POSITIVE INTRAVENOUS TECHNETIUM-99m PYROPHOSPHATE SCINTIGRAPHY – AN EARLY NON-INVASIVE MARKER OF MYOCARDIAL REPERFUSION

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Recently we found that technetium-99m pyrophosphate (Tc-PYP) accumulates in necrotic myocardium immediately after intracoronary thrombolysis and intracoronary injection into the re-opened coronary artery. To determine, whether acute Tc-PYP accumulation is also seen after intravenous (iv) application in patients (pts) with acute myocardial myocardial infarction (AMI) undergoing thrombolysis, 17 pts with AMI (symptoms < 3 hours) were studied. 10 mCi Tc-PYP were injected iv 30-60 minutes after thrombolysis, followed by coronary and left ventricular (LV) angiography. After intracoronary injection of 0.3 - 0.5 mCi thallium (Tl-201) into both coronary arteries, planar dual isotope scintigraphy and, in 7/17 pts additional emmision computed tomography (ECT) were performed. Regional and global ejection fraction were determined from acute and follow-up LV angiograms. According to the patency of the infarct artery and the size of the Tl-defect pts were devided into 3 groups.

Group	infarcted artery	Tl-201 defect	TC-PYP accumulation	regional EF % acute	regional EF % follow-up	global EF % acute	global EF % follow-up
A (n=6)	open	large >30 % of cardiac silhouette	massive	7.0 ±10.4	6.2 ± 18.3	49.8 ±11.9	44.6 ±13.7
B (n=7)	open	small (4), none (3)	focal negative	43.9* ±21.0	54.0* ± 17.9	67.4** ± 10.1	67.0* ± 9.0
C (n=4)	occluded	large	negative	9.3 ± 3.2	11.3 ± 4.9	53.3 ± 2.5	47.7 ± 2.5

*p < 0.01, **p < 0.02 (B vs A and C). These findings were confirmed by ECT in 7/17 pts.

Conclusions: 1) Early intravenous Tc-PYP scintigraphy is a reliable non-invasive method to detect myocardial reperfusion after thrombolysis in the presence of myocardial necrosis. 2) Massive early Tc-PYP accumulation after thrombolysis predicts compromised LV function at follow-up.

CORONARY ANGIOPLASTY IN THE TREATMENT OF CARDIOGENIC SHOCK: THE THERAPY OF CHOICE.

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Cardiogenic shock (CS) due to pump failure is nearly 100% fatal. Fibrinolytic therapy works slowly and often results in only partial reperfusion resulting in inadequate left ventricular recovery. We used coronary angioplasty (CA) as initial therapy in 74 patients with acute myocardial infarction (MI). Ten patients presented to the Cardiovascular Lab with CS. CS was defined as clinical evidence of systemic hypoperfusion as well as systolic blood pressure < 80 mm/Hg and pulmonary capillary wedge pressure > 30 mm/Hg. Eight patients had left anterior descending total occlusion, 1 patient had a right coronary artery occlusion and 1 patient had a circumflex graft total occlusion with all native coronary arteries as well as a right coronary artery bypass graft chronically occluded. Successful dilation was achieved in 60% of patients with CS. One patient who underwent successful CA died of pump failure one week after CA. All other CS patients after successful dilation were free of angina pectoris and congestive heart failure with only 1 requiring diuretic therapy on follow-up from 3-17 months (mean 8.6 months). Three of the patients who had unsuccessful dilation of the occluded vessel died of pump failure in the Cardiovascular Lab. The other patient continues to have symptoms of congestive heart failure and angina pectoris. This compares with a success rate of 91% in the MI group without CS who underwent acute CA. Two of the successfully dilated CS patients developed restenosis, one undergoing repeat CA, the other coronary bypass. Acute CA can be effective in some patients with CS.

THE USE OF INTRAVENOUS ANISOYL PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (BRL 26921) IN ACUTE MYOCARDIAL INFARCTION.

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We have used a new fibrin-dependent thrombolytic agent, Anisoyl plasminogen streptokinase activator complex (APSAC), to study the role of intravenous thrombolytic therapy for suspected acute myocardial infarction, in a community hospital. APSAC shares with TPA the dual advantage of high local concentration and relatively low systemic activity, but in addition it has prolonged action sustained over several hours after a single intravenous bolus. 149 patients with onset of major symptoms within 4 hr were randomised to receive either 30 mg APSAC (76, group A) or conventional treatment alone (73, group B). All had typical symptoms with ECG changes including ST segment elevation. Evolution to completed infarction occurred subsequently in significantly fewer patients treated with APSAC than in the control group (79% v 92%, $p < .05$). Discharge R wave scores of 49 in group A and 37 in group B indicated better preservation of myocardial depolarisation after APSAC ($p < .05$). Peak CK-MB enzyme levels tended to be earlier and higher in group A ($p = .08$). Fewer patients had recurrent ischaemic pain in group A than group B (47% v 63% $p = .06$). Total 7-day hospital mortality was 3 in the APSAC group and 6 in the control group. No definite serious complications were observed but one patient in the APSAC group had a shower of emboli to the lower trunk and limbs. Thus Anisoyl plasminogen streptokinase activator complex is relatively safe, simple to administer by intravenous route and shows promise for reducing myocardial damage after thrombotic occlusion.

SYMPTOMATIC AND ASYMPTOMATIC CORONARY REOCCLUSION AFTER SUCCESSFUL REPERFUSION IN RELATION TO THE INITIAL TIME OF TRANSMURAL MYOCARDIAL ISCHEMIA.

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One main limitation of reperfusion therapy in acute myocardial infarction (AMI) is the time interval between onset of angina and start of treatment. To contribute to the definition of this interval, symptoms in patients (pts) suffering either symptomatic or asymptomatic coronary reocclusion were analysed.

In 57 cases (48 ♂ and 9 ♀) pts with previously successful intracoronary thrombolysis started up to 8 hours after AMI, reocclusion was documented in the follow-up angiogram. Pts with initially subtotal occlusion of the infarct related vessel and evidence of collaterals at first or repeat angiography were excluded. All pts were followed up for clinical, electrocardiographical (ST ↑ ≥ 0.1 mV in inferior and ≥ 0.2 mV in anterior leads), enzymatic (CPK ↑) and angiocardiographical signs (Δ EF % ↓) of reinfarction. Reocclusion happened at an average of 16 days (0 – 270) after the acute intervention.

Results:

Group	Age / yrs.	Initial time of occl./min	Reocclusion: Chest-pain	Reocclusion: ECG ST ↑	Reocclusion: CPK ↑	Reocclusion: ΔEF % ↓
A (n = 10)	58 ± 15	0 - 120	10/10	10/10	8/10	8/10
B (n = 25)	56 ± 10	120 - 240	18/25	17/25	14/25	12/25
C (n = 17)	56 ± 10	240 - 360	9/17	8/17	6/17	5/17
D (n = 5)	55 ± 10	360 - 480	1/ 5	0/ 5	0/ 5	0/ 5
Σ (n = 57)	56 ± 10	0 - 480	38/57	35/57	28/57	24/57

Conclusions: If reocclusion occurs, less than 50 % of pts with an initial time of ischemia exceeding 4 hours, but almost every pt successfully reperfused within 2 hours, suffers from symptomatic reinfarction. After an initial time of ischemia longer than 6 hours, however, reocclusion usually does not cause symptoms of reinfarction. This may emphasize, that thrombolytic therapy in pts without evidence of collaterals is unlikely to salvage significant amounts of ischemic myocardium, when reperfusion is achieved later than 4 hours after onset of symptoms.

MYOCARDIAL CONTRACTILE RESERVE AFTER THROMBOLYSIS.

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The early assessment of myocardial salvage after thrombolysis is difficult due to the prolonged recovery of the stunned myocardium. In order to unmask "stunning", we sought to compare left ventricular inotropic contractile reserve of patients after successful versus unsuccessful thrombolysis. Radionuclide ventriculograms were obtained in 80 consecutive patients 2 weeks after myocardial infarction, at rest and during intravenous isoproterenol infusion. Resting and isoproterenol stressed left ventricular ejection fractions (EF) were compared in the patent and closed infarct-related vessel groups. Data are recorded as mean ± standard error.

Vessel	Number	Resting EF	Isoproterenol EF
Patent	53	0.49 ± 0.02	0.62 ± 0.02
Closed	27	0.48 ± 0.02	0.54 ± 0.02

Although there was no difference in the resting EF between the 2 groups, isoproterenol increased the EF in the patent infarct-related vessel group (0.13 ± 0.01) significantly more than in the closed infarct-related vessel group (0.06 ± 0.01) ($p < 0.0001$). Thus, 1) there was a significantly greater increase in the left ventricular ejection fraction in response to isoproterenol in patients with a patent infarct vessel as compared to a closed infarct vessel; and 2) the restoration of blood flow in acute myocardial infarction results in improved inotropic contractile reserve, suggesting myocardial salvage.

STREPTOKINASE AND NITRATES INCREASE THE FREQUENCY OF CORONARY REPERFUSION IN ACUTE MYOCARDIAL INFARCTION.

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The relative roles of thrombosis and coronary vasoconstriction in the pathogenesis of acute myocardial infarction remain poorly understood. We performed coronary arteriography in 22 patients (pts) within 4 hours of the onset of continuous chest pain associated with ST elevation. In all pts the ischemia related vessel was occluded and failed to reopen with intracoronary (IC) isosorbide dinitrate (ISDN; 2mg). Thrombolysis with IC streptokinase (5000iu/min) reestablished patency in 16 pts (in 5 within 2 hours from the onset of symptoms with no subsequent development of Q waves). During streptokinase infusion in these 16 pts, reocclusion occurred in 6 pts (group A), and in 6 other pts (group B) partial patency was associated with poor distal filling and run-off of contrast medium. Following IC ISDN the reoccluded vessel was reopened in 4 pts of group A and patency with normal filling and run-off of contrast medium was achieved in all 6 pts of group B.

Despite thrombolysis intermittent arterial reocclusion may be seen during the acute evolution of myocardial infarction. Interaction between intraluminal thrombosis and coronary vasoconstriction appears to perpetuate the coronary occlusion. Combined IC thrombolytic and nitrate therapy increases the frequency of coronary recanalisation in acute myocardial infarction.

LONG-TERM SURVIVAL FOLLOWING STREPTOKINASE THERAPY IN ACUTE MYOCARDIAL INFARCTION.

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One hundred patients (pts) aged 23-79 years (mean 52) underwent coronary and left ventricular angiography within 6 hours of onset of acute myocardial infarction (MI). Seventy pts received intracoronary and 30 intravenous streptokinase (SK). Reflow was achieved in 64 pts (64%), with persistent occlusion or reocclusion occurring in 36 (36%). Seven pts (7%) died in hospital, of whom 5 had persistent occlusion or reocclusion. Of the 89 survivors, 21 (23%) underwent coronary artery bypass surgery (CABG) and 22 (24%) coronary angioplasty (PTCA) prior to hospital discharge. There was no significant difference between mean left ventricular akinetic segment (AK) length on admission (12.4 ± 8cm) and at repeat angiography 10 days post-MI (11.1 ± 8cm). Hospital survivors were followed for 35 ± 19 months (range 1.5-70). There were only 2 late deaths, both non-cardiac. Of the remaining 91 survivors, 5 had recurrent MI, 3 in the region of previous MI. Four pts underwent CABG 3-15 months post-MI for recurrent angina.

In summary, there is an excellent long-term survival in this group of pts, despite lack of objective evidence of myocardial salvage. This survival may reflect the high incidence of post-MI intervention with CABG and PTCA.

IN-HOSPITAL COURSE OF PATIENTS ADMITTED WITH A MYOCARDIAL INFARCTION: IDENTIFICATION OF A LOW-RISK GROUP FOR DEVELOPING LIFE-THREATENING ARRHYTHMIAS. Joe Anderson, M.D., Mihai Gheorghiade, M.D., F.A.C.C., Bernard Velardo, M.D., Loni Schultz, M.S., Alan Friedman, David Goldberg, M.D., Howard Rosman, M.D., F.A.C.C., and Sidney Goldstein, M.D., F.A.C.C., Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan.

One thousand and ninety-six patients (pts) admitted to the CCU with a definite myocardial infarction were evaluated and followed prospectively throughout their hospitalization. Of these, 764 pts were considered to be in a high risk group (HRG) based upon the following characteristics obtained at the time of admission: pulmonary rales, S3 gallop, heart failure by chest x-ray, blood pressure <100 mmHg, cardiogenic shock, complex ventricular arrhythmias and high degree AV block. The remaining 332 pts were considered to be at low risk. The mean age for the low risk group (LRG) was 62.3 years and for the HRG was 62.8 years (NS).

	LRG (332 pts)	HRG (764 pts)	P=value
CCU deaths	0.3% (1)	13% (104)	<.0001
Post CCU deaths	1.8% (6)	5.3% (41)	<.007
Invasive monitoring	3% (10)	20% (158)	<.0002
Defibrillation	0%	10% (77)	<.0002
Cardioversion	0%	6% (47)	<.0002
Pacemaker Rx	1.8% (6)	14% (114)	<.002

In the low risk group no pt had to be readmitted to the CCU because of a life-threatening arrhythmia. We conclude that a LRG of pts can be defined based upon admission clinical criteria. They have a low likelihood of life-threatening arrhythmias during hospitalization and could be admitted to an intermediate care unit reducing admissions to the CCU by 30% without compromising patient care.

ISIS COLLABORATIVE GROUP: RANDOMIZED TRIAL OF EARLY IV ATENOLOL IN MYOCARDIAL INFARCTION; SUBSIDIARY ANALYSES

ISIS Collaborative Group, Radcliffe Infirmary, Oxford, England (Chairman P.Sleight, D.M., F.R.C.P., Co-ordinator R.Collins, M.B. B.S., M.Sc.)

16048 patients, admitted to 250 hospitals with suspected myocardial infarction (MI) were randomized to receive either immediate IV atenolol followed by oral atenolol for 7 days or routine coronary care treatment. There was no apparent reduction in the probability of a 2x enzyme elevation or in cardiac arrest, a moderate but non-significant reduction in non-fatal reinfarction and an increase in non-fatal heart block; 1-2% extra required inotropes (but survived).

Prognosis and apparent mortality reduction was similar for patients entering 0-4, 5-8, 9+ hours after onset (mean = 5 hrs). No clear interaction of proportional risk reduction with initial age, HR, SBP, ECG findings or history of MI or diabetes was found.

To check for early hazards of beta-blockade (days 0-1) or withdrawal effects (after trial treatment stopped on day 7), early mortality was split (0-1, 2-3, 4-5, 6-7, 8-9 days): no effect whatever was apparent except in days 0-1, where all the apparent benefit was concentrated (170/8002 control deaths, 118/8048 atenolol).

BETA-BLOCKER POOLING PROJECT ; SUBGROUP FINDINGS IN POST-MYOCARDIAL INFARCTION PATIENTS.

BETA-BLOCKER POOLING PROJECT GROUP. Presented by Alain LEIZOROVICZ, M.D., Unité de Pharmacologie Clinique, Lyon, France.

The objectives of beta-blocker pooling project (BBPP) was to collect data from large long-term late entry (24 hours or more) clinical trials of beta-blockers (B) in post-infarction (MI) patients (PTS) in order to conduct subgroup analyses for which the individual trials had inadequate power. 1 year all cause mortality data from 9 trials involving more than 13,700 PTS were obtained. Overall, mortality was 25 % lower in the B group compared to the placebo controls. However, statistical tests suggested some heterogeneity between the trials, which tested 7 different B. There was no evidence that treatment outcome was related to sex, baseline level of heart rate (range 50-90) or blood pressure or the time at which treatment was initiated (usually 5 to 14 days). In contrast, subgroups with high placebo group mortality (history of previous MI, angina, mechanical or electrical complications or digitalis usage) benefited clearly from treatment with homogeneous outcomes from the pooled trials whereas in the complementary subgroups results were not homogeneous.

In conclusion, BBPP indicates that high risk MI PTS without contra-indications are the prime candidates for B therapy.

INFARCT SIZE AND CONDUCTION SYSTEM INVOLVEMENT IN ACUTE ANTERIOR AND POSTERIOR INFARCTS WITH COMPLETE HEART BLOCK

Maria-Dorina C. Sevilla, M.D., Donald B. Hackel, M.D., Eileen M. Mikat, Ph.D., Keith A. Reimer, M.D., Ph.D., Raymond E. Ideker, M.D., Ph.D., Zoltan G. Turi, M.D., MILIS Group, Duke University Medical Center, Durham, North Carolina

This study determined the differences between myocardial infarct (MI) size, degree of conduction fiber necrosis and/or hydropic degeneration, and clinical presentation and outcome in patients with acute anterior (AMI) and acute posterior infarcts (PMI) with and without complete heart block (CHB) who came to autopsy. The hearts from 46 patients were grouped into: I-AMI with CHB (8), II-AMI without CHB (13), III-PMI with CHB (19), and IV-PMI without CHB (6). In each heart, areas of MI were identified on histologic sections and infarct size was measured (% of LV) using a digitizer and computer. Necrosis and hydropic degeneration in the conduction system were graded from 0 to +4. Clinical diagnosis and location of acute MI were determined by ECG and serum enzyme levels. CHB was considered present if seen on any one ECG tracing post MI. The infarct size of I (42.8%±8.5) was significantly larger than III (24.1%±10.4) ($p<.001$). Conduction fiber necrosis occurred in the common bundle and bundle branches in I and in the approaches to the atrioventricular node (AVN), AVN itself, common bundle and posterior left bundle in III. Although only focal necrosis of 2+ in I and 2 to 3+ in III was noted, hydropic degeneration ranged from 2 to 3+ in I and III, and the adjacent myocardium showed 4+ necrosis in both groups. No conduction tissue necrosis was seen in II and IV. The onset of CHB post MI occurred with a mean of 2 days in I and 6 days in III where it was often transient. Thus, AMI's with CHB are larger; CHB occurs sooner and is more persistent and necrosis involves the more anterior portions of the conduction system. In the smaller PMI's with CHB, CHB occurs later, may be transient and necrosis involves the more posterior portions of the conduction system.

DIFFERENTIAL INCIDENCE OF WALL MOTION ABNORMALITIES AND RESIDUAL MYOCARDIAL JEOPARDY IN NON-Q-WAVE INFARCTIONS.
Joe K. Bissett, M.D., F.A.C.C., John Matts, M.D., Henry Buchwald, M.D., and the POSCH Study Group, Univ of Arkansas for Medical Sciences, Little Rock and Univ of Minnesota Medical School, Minneapolis.

The purpose of this study was to compare the incidence of residual myocardial jeopardy in patients with non-Q and Q-wave infarctions. Abnormal wall motion and coronary anatomy were determined in 486 patients with stable symptoms for at least 6 months following a single anterior (A=40) or inferior (I=35) non-Q-wave infarction and compared with 411 similar patients after a Q-wave infarction. Abnormal wall motion was measured from a ventriculogram in the right anterior oblique position in 4 anterior-apical and 2 inferior segments. Results include abnormal wall motion expressed as % segments without retained wall motion in infarcted area (%AWM), number of patients with/without retained wall motion (normal hypokinetic) distal to coronary lesions >50% but <100% (jeopardized myocardium=JEPM), global ejection fraction (GEF), and collaterals.

	ANT NON Q	INF NON Q	ANT Q	INF Q
N	40	35	158	253
%AWM Segments	.03±.10*	.20±.35	.33±.32	.42±.43
JEPM Patients	20/20**	9/26	28/130	47/206
GEF	65±12*	63±9*	52±14	57±11
Collaterals	20/20	19/16	81/77	171/82*

*p<.01 vs all other groups; **p<.05 vs inferior non-Q and p<.01 vs all other groups. Conclusions: patients with anterior non-Q infarctions have 1) a significantly decreased incidence of severe wall motion abnormalities, 2) increased incidence of jeopardized myocardium, 3) ECG patterns predict the incidence of abnormal wall motion in non-Q infarctions.

IMPROVEMENT OF MYOCARDIAL METABOLISM IN PERI-INFARCT ZONES INDUCED BY NIFEDIPINE IN PATIENTS WITH INFARCTION.
Edward M. Geltman, M.D., F.A.C.C, Burton E. Sobel, M.D., F.A.C.C., and Allan S. Jaffe, M.D.,F.A.C.C. Washington University School of Medicine, St. Louis, MO.

To determine whether nifedipine can improve myocardial metabolism in jeopardized zones undergoing infarction, we performed a double-blind, randomized, placebo-controlled trial in which regional myocardial metabolism was assessed by positron emission tomography with intravenous carbon-11 (^{11}C) labeled palmitate, ventricular function by radioventriculography (RVG), and infarct size by serial MB CK analysis. Immediately after initial tomographic and RVG studies performed at admission, nifedipine (20 mg) or placebo was given q 4 hr for 48 hr as tolerated and tapered over the next 7 days. Tomography and RVG studies were repeated on day 10. Infarct size and initial ejection fraction were indistinguishable between groups. The estimated extent of impaired ^{11}C-palmitate accumulation declined from 58 ± 8 (SD) g-eq to 49 ± 7 in treated patients ($p < .05$) but did not change at all in controls (44 ± 9 initially and 44 ± 12 after 10 days). Ejection fraction decreased by an average of 16% of baseline in controls but remained constant (51 ± 6 and 50 ± 5%) in treated patients. Thus, despite the lack of gross reduction of infarct size, nifedipine initiated early after the onset of infarction exerts salutary effects on regional myocardial metabolism in the peri-infarct zone compatible with decreased afterload, reduced coronary spasm, direct myocardial protection, or combinations of the three.

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AUTONOMIC NEUROPATHY CAUSES IMPAIRMENT OF THE HEMODYNAMIC RESPONSES TO EXERCISE IN DIABETICS WITHOUT ISCHEMIC HEART DISEASE.
Joel K. Kahn, M.D., Benjamin Zola, M.D., Jack Juni, M.D., Aaron I. Vinik, M.D., University of Michigan, Ann Arbor.

Abnormal hemodynamic responses to exercise have been observed in diabetics. We hypothesized that autonomic neuropathy (AN) contributed significantly to these alterations. We studied 32 long-term (≥10 years) insulin-dependent diabetics without clinical evidence of cardiac disease by graded treadmill exercise testing. Two of the 32 had occult ischemic heart disease by stress and reperfusion thallium scintigraphy and were excluded from subsequent analysis. Of the remaining 30 subjects, 17 had AN by a battery of cardiovascular reflex testing. We compared the responses to exercise of the 17 subjects with to the 13 subjects without AN. At rest the pressure rate product (PRP) was higher in those with AN (114.0±5.7 vs. 95.9±5.3,p<.05). With maximal exercise the increase in heart rate (44.6±4.8 vs. 79.0±5.4 beats/minute,p<.001), systolic blood pressure (36.8±5.9 vs. 55.0±5.8 mmHg,p=.02) and the PRP (98.0±7.3 vs. 182.0±8.2,p<.001) were all lower among those with AN despite similar total treadmill times (631±47 vs. 587±40 seconds,p>.10). At each stage of exercise the increase in heart rate and systolic blood pressure was lower (p<.05) among the diabetics with AN. The severity of AN correlated inversely with the maximal increase in heart rate (r=-.68,p<.001) and PRP (r=-.58, p<.005). Age, duration of diabetes mellitus and the presence and severity of microvascular complications did not correlate with any of the hemodynamic parameters. Thus, AN is a cause of the profound impairment of the hemodynamic responses to exercise in diabetics without ischemic heart disease.

DOES EXERCISE CAUSE PROLONGED REDUCTION OF ALPHA-ADRENERGIC RESPONSIVENESS OR ALTER POST-EXERCISE BAROREFLEX FUNCTION?
Michael Maddens, M.D., Robert Levine, B.A., Josef Gurian, B.S., David Mendelowitz, B.S., Thomas Lincoln, B.A., and Jeanne Y. Wei, M.D., F.A.C.C., Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts.

To test the hypothesis that exercise (EX) may alter the arterial response to α-adrenergic stimulation, we studied 12 adult (5-9 mo) male rats with chronic indwelling venous and arterial catheters. In 6 rats the mean arterial pressure response (ΔMAP) to bolus (16 ug/10 s) IV phenylephrine (PE) was measured before EX. After a 30 min EX (rodent treadmill, 0.9 km/hr, 0° elevation) the ΔMAP was measured in response to serial boluses of PE at 15, 30, 45, and 60 min post-EX, and was compared to pre-EX ΔMAP in paired samples.

	15 min	30 min	45 min	60 min
post/pre-EX ΔMAP	66% *	51% **	84%	95%

In six other rats, studies were performed using variable doses of PE to obtain 4 sequential 10 mm Hg rises in MAP. The PE dose needed to reach target ΔMAP's was determined pre-EX. Then, sequential infusions were performed at 15, 30, 45, 60, and 75 min post-EX. The dose (ug) of PE needed to reach target ΔMAP's was determined at each time post-EX, and using paired samples, was compared to the pre-EX dose.

ΔMAP	15 min	30 min	45 min	60 min	75 min	
10 mm Hg	+2 *	+3 *	+2	+4**	+2 *	*=(p<.05)
20 mm Hg	+11 *	+7 *	+4 *	+4 *	+4 *	**=(p<.01)
30 mm Hg	+12 *	+9***	+4 *	+4 *	+5 *	***=(p<.001)
40 mm Hg	>+17**	>+15**	+5	+5	+4	

Finally, when MAP was plotted against RR interval ($\overline{RR}$), the ΔMAP to the major inflection point was smaller at 15 min (p<.01) and 30 min (p<.025).

Thus, exercise diminishes responsiveness to α-adrenergic stimulation for ≥75 min, and improves baroreflex function. These findings suggest that exercise may give prolonged protection against arterial pressure elevation.

A NEW STRESS TESTING TECHNIQUE, NONINVASIVE TRANSTHORACIC PACING TACHYCARDIA: COMPARISON TO EXERCISE STRESS TESTING. MD Feldman, EV Gervino, JM Aroesty, FACC, HD Royal, JA Parker, KJ Silverman, FACC, RC Pasternak, FACC, W Grossman, FACC, PM Zoll, FACC, R McKay. Harvard Thorndike Laboratory, Beth Israel Hospital, Boston, MA

Improvements in noninvasive (NI) external ventricular pacing (PAC) have led to a technique with reliable electrical capture and minimal patient discomfort. We applied this technique in combination with thallium-201 scintigraphy (TI) to 9 patients (pts) referred for coronary angiography. TI after NI PAC was compared with TI after an exercise treadmill test (ETT). Pts were NI paced to greater than 85% of age predicted maximum heart rate, and underwent maximal exercise to a respiratory exchange ratio >1.0. The paced and exercised groups achieved similar rate pressure product (RPP X 10^3) at onset (15.1 ± 2 versus 15.3 ± 2) and termination (12.5 ± 2 versus 11.9 ± 1) of angina, and similar maximal RPP (19.5 ± 1 versus 21.6 ± 3), respectively. NI PAC produced reversible TI defects in all 8 patients with coronary artery disease (CAD) and no defect in the patient with normal coronaries. ETT produced reversible TI defects in only 4, normal TI in 3 despite CAD, and a fixed TI defect in 1 with CAD. We conclude that NI PAC with TI may be comparable to ETT in detecting CAD. This new modality warrants further study for pts unable to undergo the exercise required for standard ETT.

CARDIOVASCULAR COMPLICATIONS OF OUTPATIENT CARDIAC REHABILITATION PROGRAMS

Steven P. Van Camp, M.D., F.A.C.C., Richard A. Peterson, Ph.D., San Diego State University, San Diego, California

To determine the incidence of major cardiovascular complications which occurred within the conduct of outpatient cardiac rehabilitation programs from January, 1980, through December, 1984, we surveyed a random sample of America's cardiac rehabilitation programs. Programs were identified from American Heart Association, California Society for Cardiac Rehabilitation, YMCARDIAC Therapy, and Cardiac Treatment Center directories. A random sample of 150 operational outpatient programs received a questionnaire and a follow-up phone call. Programs were categorized by the degree of ECG monitoring during exercise sessions as continuous, intermittent or graduated. Graduated programs monitored new patients continuously for at least three exercise sessions before progressing to intermittent monitoring. Data was obtained from 115 programs. Seven programs responding had continuous and intermittent programs resulting in data from 122 programs.

Complications during or related to exercise sessions: (incidence per 10^6 patient-hours in parentheses)

Program Type	n	Patient-Hours	Cardiac Arrests	Myocardial Infarctions	Fatalities
Continuous	74	719,436	9 (12.5)	4 (5.6)	0
Intermittent	37	811,096	7 (8.6)	2 (2.5)	3 (3.7)
Graduated	11	180,545	2 (11.1)	4 (22.2)	1 (5.5)
Total	122	1,711,077	18 (10.5)	10 (5.8)	4 (2.3)

Conclusions: Within the survey period there was a low incidence of major cardiovascular complications during or related to prescribed supervised exercise in cardiac rehabilitation programs. The incidence was similar regardless of the type of program.

SELF-MONITORED HOME-BASED MODERATE INTENSITY EXERCISE IN MEN AND WOMEN: EFFECTS ON FUNCTIONAL CAPACITY

Martin Juneau, MD, Flay Rogers, BA, Victoria deSantos, PA, Martin Yee, BA, Anthony Evans, PhD, Andrea Bohn, BA, William L. Haskell, PhD, FACC, Craig B. Taylor, MD, Robert F. DeBusk, MD, FACC, Stanford Medical Center, Stanford, CA

Moderate intensity exercise performed in supervised groups significantly increases maximum oxygen uptake(VO2max). This study was designed to evaluate the effectiveness of a self-monitored home-based exercise program in increasing VO2max in 60 men aged 49±6 and 60 women aged 47±5. These healthy sedentary subjects were randomized to a control(C) or exercise(E) group which trained at 65-72% of pre-training peak heart rate for a duration that resulted in a caloric expenditure of approximately 300kcal/session(mean 51±8min)5x/wk. A heart rate(HR) monitor was used to regulate training intensity. A solid-state microprocessor recorded HR and physical activity for 3 consecutive days. Daily logs were used to record frequency, intensity and duration of training.

CHANGE IN VO2MAX(ML/KG/MIN) AFTER 12 WEEKS OF TRAINING:

Group	N	Baseline VO2max	12 Weeks VO2max	Difference	%Diff.	P
Exercisers						
Male	28	31.8	35.8	+4.0	+13.0	<.001
Female	28	25.8	28.1	+2.3	+ 9.0	<.001
Controls						
Male	26	32.8	32.6	-0.2	- 0.2	NS
Female	25	26.6	25.9	-0.7	- 2.5	NS

The mean increase in VO2max was 44% higher in men than in women ($p<.05$). Adherence to training defined by a combination of frequency, intensity, duration of sessions and number of weeks in program exceeded 90% in men and women. CONCLUSIONS: Self-monitored home-based moderate intensity exercise training is as effective as supervised group training in increasing VO2max in sedentary healthy individuals.

EXERCISE INDUCED SUSTAINED VENTRICULAR TACHYCARDIA IN YOUNG HEALTHY ADULTS: CLINICAL, ELECTROPHYSIOLOGIC FINDINGS, AND TREATMENT

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Exercise induced ventricular tachycardia (EIVT) has been reported to adversely effect prognosis. Clinically sustained monomorphic VT is reproducible utilizing standard electrophysiologic stimulation (EPS) techniques in a majority of patients. We wish to report on 12 patients (pts), average age = 23.6 yrs (20-26 yrs) who demonstrated reproducible sustained EIVT (cycle length 285-350 msec) on exercise testing (ET). No pt had chest pain or ST segment changes during ET, but 6 developed symptomatic hypotension. In ten of the 12 pts undergoing cardiac catheterization, normal coronary anatomy before/after ergonovine was found. Left ventricular function was normal in all pts. In all 12 pts, EPS studies were negative (3 right ventricular sites/2 cycle lengths/ 3 extrastimuli) until isoproterenol (I) was administered. During I administration to 4mg/min, all 12 pts developed VT without electrical stimulation. Treatment with B-blocking agents for a mean of 22 months (10-32) has prevented EIVT and I induced VT in all pts. In conclusion, in 12 young adults with sustained EIVT: (1) there was no associated cardiac disease; (2) ET or I infusion reproduced VT in all pts while standard EPS was negative; (3) treatment with B-blocking agents prevents EIVT in follow-up.

VENTRICULAR DEPOLARIZATION LATE POTENTIALS RECORDED BY SIGNAL-AVERAGING PREDICT EXERCISE-RELATED VENTRICULAR ARRHYTHMIAS.

Kn Hai Han, M.D.; James Cameron, M.D.; Thomas F. Deering, M.D.; Modestino G. Criscitiello, M.D., F.A.C.C.; Linda Woodbury; Beverly Cobb; N. A. Mark Estes, III, M.D., F.A.C.C. Tufts-N. E. Med. Center, Boston, MA.

To investigate the relationship of ventricular depolarization late potentials to the development of exercise-related ventricular arrhythmias (VA), signal-averaged vectorcardiograms (SAV) were performed in 54 patients (pts) before and immediately after exercise stress testing (Bruce protocol). Pts included 33 males and 21 females aged 55±12 yrs (mean ± S.D.); including 23 pts with ischemic heart disease. No pt had clinical ventricular tachycardia (VT) or was taking antiarrhythmic drugs for VA. SAV were recorded using bipolar X, Y, Z leads with bandpass filters of 25, 50-300 Hz. LP were defined by the combination of QRS duration >130 msec and terminal amplitude (TA) (40 msec prior to QRS offset) <35 μv at 25 Hz high pass filter (HPF) and QRS duration >115 msec and TA <25 μv at 50 Hz HPF at rest or during exercise. Exercise-related VA were defined as an increase or emergence of frequent or multifocal ventricular premature beats, couplets or VT during exercise or recovery phase compared with baseline. Rhythm was monitored for at least 3 minutes prior to exercise, during exercise and in the recovery phase (<6 min.). Results for pts with VA during exercise and recovery (Group I) and with VA during exercise (Group II) are as follows:

	Group I (54 pts)		Group II (50 pts)	
	LP Present	LP Absent	LP Present	LP Absent
VA Present	9	3	8	0
VA Absent	6	36	6	36

Group I: Sensitivity=75%, Specificity=86%, Positive predictive accuracy=60%, Negative predictive accuracy = 76%. Group II: Sensitivity = 100%, Specificity = 86%, Positive predictive accuracy = 58%, Negative predictive accuracy = 100%.
Conclusions: 1) LP recorded by SAV are predictive of exercise-related VA. 2) This association is stronger in pts with VA during the exercise phase.

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CATHETERIZATION DOES NOT ADD TO CLINICAL AND TREADMILL DATA FOR PREDICTING PROGNOSIS IN LOW-RISK PATIENTS

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To identify patients undergoing treadmill testing (TM) in whom results of cardiac catheterization (CATH) do not alter predicted prognosis, we studied 2,722 consecutive patients (pts) who had a Bruce TM and CATH within 6 weeks. Pts were followed for up to 10 years (median follow-up 5 years). Surgically treated pts (n=627) were censored at the date of operation. All exercise-induced ST deviation ≥ .10 mV was measured using a calibrated grid. Five clinical and 2 TM variables were independent prognostic factors in these pts: summary measures of myocardial damage, angina severity and extra-cardiac vascular disease, sex, age, amount of exercise ST deviation, and exercise duration. In the overall population, additional prognostic data at CATH was obtained from the ejection fraction, amount of left main and proximal left anterior descending stenosis and number of stenosed (≥ 75%) coronary arteries. CATH data changed Cox model predicted 5 year survival by ≤ .01 in 1013 pts (37%). In this latter group, a low-risk subset could be defined on clinical grounds: no CHF; no resting Q waves; stable pain course; exercise ST deviation < .20 mV; and exercise duration > 6 minutes. In this subset of 844 pts (31%), there were 6 left main pts (<1%), 58 3 vessel disease pts (7%) and 9 pts with an ejection fraction ≤ 40 (1%). The majority of pts had ≤ 1 vessel disease and normal LV function.

In conclusion, it is possible to identify a low-risk group of pts using clinical and exercise data in whom very little added prognostic information is obtained from catheterization.

EFFECTS OF CORONARY REVASCULARIZATION ON EJECTION FRACTION AND ABNORMALLY DOCUMENTED DIASTOLIC BLOOD PRESSURE RESPONSE TO EXERCISE TESTING

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Twenty six patients with coronary artery disease and an abnormal diastolic blood pressure response to treadmill exercise (elevation > 15 mmHg) were exercised before and after coronary bypass surgery. In addition 17 of these patients underwent graft restudy at a mean time of 15 ± 1.5 months post surgery. Following surgery the mean ejection fraction improved from 55% ± 3.4 to 68% ± 3.1 ($p < 0.001$). Eleven patients had a negative preoperative stress test by ST segment but had a significantly lower ejection fraction pre operation than those with abnormal ST segments (49% ± 2.8 v 64% ± 4.8 $p < 0.001$). Patients were exercised at 2 weeks and 3, 6 and 12 months after surgery. With the improvement in ejection fraction the diastolic blood pressure response to exercise reverted to normal.

However, an abnormal diastolic blood pressure response recurred in 4 patients, 3 of whom also developed ST segment depression on exercise. Graft occlusion and a reduced ejection fraction was demonstrated at angiography in all four. The graft patency rate in the 17 patients studied was 83% at 15 months.

Conclusion: A reduction in ejection fraction is probably responsible for the abnormal diastolic blood pressure response which occurs earlier than ST segment depression during exercise testing. The mechanism is probably reflex vasoconstriction secondary to a falling cardiac output. When coronary bypass surgery improves the ejection fraction normalization of the diastolic blood pressure response follows.

THE EFFECTS OF PROLONGED UNILATERAL FOREARM IMMOBILIZATION ON MAXIMAL PERIPHERAL BLOOD FLOW.

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We studied the effects of prolonged forearm casting on maximal peripheral blood flow in an effort to determine whether peripheral immobilization leads to reduced local vasodilator capacity. The subjects (n=4) were studied within hours of removal of forearm casts applied for fractured forearms or wrist bones. The forearms were immobilized for at least 30 days prior to study. Forearm blood flow (FBF) (ml/min·100ml) was measured in both arms of each subject using a strain-gauge plethysmograph (venous occlusion technique). In addition to basal FBF, the blood flow response after release of 5 minutes of arterial occlusion, the peak reactive hyperemic blood flow response (RHBF), was measured as an index of vasodilator capacity. Minimal resistance (R) and maximal conductance (C) were derived from the RHBF and mean BP.

	Casted Arm	Control Arm
Basal FBF	3.0 ± .5	1.8 ± .4
RHBF	29.6* ± 2.4	37.7 ± 4.4
R	3.5* ± 8.4	2.8 ± .4
C	.29* ± .05	.39 ± .03
FC	25.8 ± .9	27.0 ± 1.1

*p<.05 vs control, FC=Forearm circumference(cm)

These results demonstrate that unilateral, prolonged, peripheral immobilization reduces localized maximal vasodilator capacity. Thus, the peripheral circulation participates in the detraining process associated with immobilization.

CARDIAC DYNAMICS DURING SUPINE EXERCISE FOLLOWING HEART TRANSPLANTATION: ASSESSMENT BY RADIONUCLIDE ANGIOGRAPHY

Peter W. Pflugfelder, MD, Paul D. Purves, F. Neil McKenzie MD, William J. Kostuk MD, FACC, University Hospital, London, Ontario, Canada.

The mechanisms by which the denervated heart responds to supine exercise were examined in 20 cardiac transplant (TP) recipients 1 to 25 mo (mean 11.6 mo) following surgery. Results were compared to 15 normal subjects (N). Left ventricular volumes were determined by equilibrium gated radionuclide angiography at rest and during graded (25 w increments), symptom limited supine bicycle exercise. Responses to exercise are shown below:

	Ex Dur (min)	Heart Rate Rest	Heart Rate X1	Cardiac Index (l/min/m^2) Peak	Cardiac Index (l/min/m^2) Rest	Cardiac Index (l/min/m^2) X1	Cardiac Index (l/min/m^2) Peak
Normals	13.0±.8	67±3	90±3	132±5	3.3±2	4.6±.2	7.6±.4
TP	11.3±.9	86±3*	89±3	116±5◊	3.6±.2	4.3±.2	5.7±.3◊

TP exhibited only a slight change in HR during X1 compared to a 34% increase in N ($p<.001$). Cardiac index (CI) rose comparably in both groups during X1 although by different means:

	Δ Stroke Index (ml/m^2) Rest to X1	Δ End systolic index (ml/m^2) Rest to X1
Normals	+3.1±3.0%	-10±3.9%
TP	+19.9±2.9%*	+4.7±3.5%◊

means given ±SEM; X1 = exercise stage 1; *$p<.001$ vs N, ◊$p<.01$ vs N.

An increase in the stroke index (SVI), mediated mainly by an increase in the end diastolic index (EDI) accounted for the rise of CI in TP. The brisk decrease in the end systolic index (ESI) seen in normals was not observed in TP and remained essentially unchanged until post exercise. In contrast, SV and EDV remained unchanged in N, the rise in CI resulting from an increase in HR. In TP the SV plateaued after the initial rise during X1 and because peak HR was lower in TP peak CI was less than in N.

These data support the concept that in TP, the rise in cardiac output during early exercise occurs by augmented preload. Systolic performance as judged by ESI response to exercise may be diminished by cardiac denervation and peak exercise CI may be less due to limited preload reserve and blunted chronotropic response.

POST EXERCISE VITAL CAPACITY: A USEFUL SUPPLEMENT TO EXERCISE ELECTROCARDIOGRAPHY FOR THE RECOGNITION OF FUNCTIONALLY SEVERE CORONARY ARTERY DISEASE

Helmut W. Lange, MD, Hugo E. Saner, MD, Anthony M. Cook, MD, Fredarick L. Gobel, MD, FACC, Claus A. Pierach, MD, University of Minnesota, Abbott-Northwestern Hospital, Minneapolis, MN

To assess whether post exercise spirometry could improve the recognition of coronary artery disease (CAD) with significant exercise-induced left ventricular dysfunction (EXLVDF, defined as a fall in ejection fraction of at least 5%), we measured the forced vital capacity (FVC) before and immediately after supine bicycle exercise in 47 subjects (5 normal volunteers [NV] and 42 patients (PTs) undergoing exercise electrocardiography (EXECG), exercise radionuclide ventriculography (EXRNV) and coronary angiography for suspected CAD).

The mean change in FVC (±1SD) from rest to exercise was +1±2% in NV, 0±7% in 10 PTs without CAD, +1±6% in 13 PTs with CAD but without EXLVDF. In contrast, the mean FVC fell by 5±9% ($p<0.02$) in 19 PTs with CAD and EXLVDF.

The use of a >2% fall in FVC with exercise as a criterion for the recognition of CAD with EXLVDF had a sensitivity of 63%, specificity of 74% and predictive accuracy (PA) of 69%, which compared favorably with the PA of EXECG-criteria (≥1mm ST-segment depression or a maximum workload ≤50 Watt), whose PA were 64% and 71%, respectively. The highest PA (76%) was achieved by a combination of both EXECG-criteria and the post exercise FVC.

We conclude that changes in FVC with exercise can be used as a supplement to the EXECG for the identification of PTs with CAD and significant EXLVDF by RNV.

MECHANISM OF CARDIAC OUTPUT INCREASE DURING DYNAMIC EXERCISE IN CARDIAC TRANSPLANT PATIENTS

S. Yusuf[1,2], J. Aikenhead[1], S. Theodoropoulos[1], N. Dhalla[1], J. Wittes[2], M. Yacoub[1]. Harefield Hospital, Middlesex, England and NHLBI, Bethesda

Mechanisms by which cardiac output (CO) increases during dynamic exercise (EX) was assessed in 17 cardiac transplant (CT) patients at rest, during volume loading (leg elevation), and exercise on a bicycle ergometer at 15 and 45 watts. Heart rate (HR), systolic and diastolic blood pressure (SBP-DBP), end-diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) ejection fraction (EF) and CO were measured by radionucleide angiography. Data are expressed as mean ± 1 SEM. (*$p<0.05$ **$p<0.01$)

	Rest	Leg Raising	15W	45W
HR	97±2	95±2	97±2	106±3*
SBP	126±3	132±4	141±5*	151±6**
DBP	82±3	84±3	86±4	91±7*
EDV	106±7	116±8*	127±9**	129±8**
ESV	39±3	42±3	44±4	43±4
SV	67±5	75±6*	83±7**	87±7**
EF	.66±.02	.67±.02	.68±.02	.70±.03
CO	6.5±.4	7.05±.5*	7.9±.6**	9.1±.7**

Conclusions: During volume loading and mild EX, increase in EDV and SV with little change in ESV or HR is the chief mechanism increasing CO. During more severe EX, further increases in CO are mediated by increased HR. Throughout, there is little change in EF. These responses differ from those reported in normal individuals and suggests that the denervated heart is more dependent on a Frank-Starling mechanism.

DIASTOLIC DYNAMICS DURING EXERCISE

Luigi Meloni,M.D,Pierpaolo Giua Marassi,M.D.,Giovanni Cioglia,M.D.,Angelo Cherchi,M.D.,Institute of Cardiology, University of Cagliari,Italy.

To assess left ventricular (LV) diastolic dynamics during exercise, simultaneous recordings of echo-phono-electrocardiogram were performed at rest and during sitting bicycle exercise (IO watts/min) in IO normal subjects, male, aged 26±3.4 years (mean±SD). Isovolumic relaxation time (IRT, from the aortic closure sound to the mitral valve opening), LV filling time (LVFT, from the onset of mitral valve opening to the mitral valve leaflet coaptation), LV end-diastolic, end-systolic dimension (ESD) and shortening fraction (SF) were measured. At rest IRT increased from supine (54.6±IO.8 msec) to sitting bicycle position (70.7±7.2 msec, $p<0.00I$). During exercise IRT shortened progressively and significantly (I8.8±5.6, at peak exercise, HR I75 beats/min, $p<0.00I$). LVFT decreased from supine (575±IOI msec) to sitting bicycle position (438±I03 msec, $p<0.00I$) and during exercise showed a further decrease (I47±IO msec, at peak exercise, HR I75 beats/min, $p<0.00I$). When compared with the indexes of systolic function, IRT was directly related to LV ESD ($r=0.62$, $p<0.00I$) and inversely related to LV SF ($r=-0.60$, $p<0.00I$). Thus, the progressive decrease of IRT during exercise appears to be related to the concomitant increase of LV systolic shortening, according to the positive influence of cardiac contractility on the rate of myocardial relaxation.

Wednesday, March 12, 1986
Poster Displayed: 2:00PM–5:00PM
Author Present: 2:00PM–3:00PM
Hall D, Georgia World Congress Center
Exercise Physiology and Testing

COMPARATIVE EFFECTS OF β-BLOCKADE, CALCIUM ANTAGONISM,AND THEIR COMBINATION ON MAXIMAL EXERCISE PERFORMANCE IN PHY= SICALLY ACTIVE MEN.

Neil F. Gordon, M.B.B.Ch., Johan P. van Rensburg, M.Sc., and Dirk P. Myburgh, M.B.Ch.B., F.A.C.C., Institute for Aviation Medicine, Pretoria, South Africa.

When selecting an antihypertensive drug for physically ac= tive patients it is essential to consider its effect on effort tolerance. The purpose of this study was to compare the effect of β-blockade, calcium antagonism, and their combination on maximal performance in physically active men, and to establish the ventilatory responses to graded treadmill testing that accompany dual β-blockade and cal= cium antagonism. Clinically used doses of propranolol (PROP), atenolol (ATEN), nifedipine (NIFED), PROP+NIFED, and ATEN+NIFED were administered with placebo for 4d each to 12 healthy, physically active, young men. Maximal per= formance was reduced to a greater degree ($p<0.05$) with PROP (8.8%,$p<0.001$) and PROP+NIFED (11.1%,$p<0.001$) than with ATEN (3.2%,$0.05<p<0.1$), NIFED (2.1%,$p<0.05$), or ATEN+ NIFED (3.9%,$p<0.01$). Maximal performance and chronotropic and ventilatory responses to maximal work were equivalent with a β-blocker and its combination with NIFED. At sub= maximal exercise, β-blockade reduced the heart rate and O_2 consumption; NIFED accentuated the heart rate but did not alter ventilation; all drugs modified the relative O_2 consumption corresponding to 85% of the maximal heart rate; and physiologic responses during dual β-blockade and calcium antagonism were similar to those with β-bloc= kade alone. This study concludes that ATEN, NIFED, and ATEN+NIFED, in contrast to PROP and PROP+NIFED, induce only minor impairments in the maximal performance of physically active men. Furthermore, chronotropic and ventilatory responses to exercise testing during dual β-blockade and calcium antagonism can be predicted from that during β-blockade.

RAPID CHANGES IN BETA ADRENERGIC RECEPTOR NUMBERS AFTER EXERCISE IN SEDENTARY AND TRAINED SUBJECTS.

Margaret R. Eisinger, M.D., Richard S. Engelmeier, M.D., Patrick J. Scanlon, M.D., F.A.C.C., Loyola University Medical Center, Maywood, Illinois.

Although various conditions are known to alter beta adren= ergic receptor numbers (BAR), the rate of change of human BAR is unknown. Since chronic submaximal exercise train= ing regulates lymphocyte BAR, we evaluated acute changes occurring in lymphocyte BAR after maximal treadmill exer= cise in 9 healthy subjects. Five sedentary individuals (S) were otherwise similar to 4 actively exercising sub= jects (EX) in age (30±2.3 vs 30±2.5), sex (3 vs 4 male), occupation and absence of medication. All subjects exer= cised to exhaustion by the Bruce protocol, and had lympho= cyte BAR measured immediately before and after exercise. Lymphocytes were separated from 25cc of blood across a Ficoll-Hypaque density gradient at 70-80% efficiency. BAR was measured by incubating membrane preparations with 7 dilutions of I^{125} cyanopindolol in the presence or absence of 1uM(-) propranolol in a total assay volume of 450ul. BAR was standardized to Lowry-Peterson protein at rest (RBAR fm/mg) and exercise (ExBAR fm/mg) and to lymphocyte number at rest (RBAR fm/lym) and exercise (ExBAR fm/lym) and expressed as mean ± SD:

GROUP	RBARfm/mg	EXBAR fm/mg	RBARfm/lym	EXBARfm/lym
S	73±24	***256±22	1461±341	***3531±721
Ex	46±30	***142±30	1302±24	***2646±705

*p=NS, **p<.005, ***p<.001

Maximal exercise was significantly better in trained (18.6 ±1min) vs sedentary (14.5±3min) subjects ($p<.05$). KD did not change after exercise, and specific binding was 86±9%. Conclusions: 1) BAR increase 2-3 times above control after exercise and this increase is independent of exercise in= duced lymphocytosis. 2) BAR increase is less in Ex than in S subjects, even though the former exercise longer.

PERSISTENT ABNORMALITIES IN SEGMENTAL MYOCARDIAL CONTRAC= TILITY IN "WALK THROUGH ANGINA",

Stephen A. Stowers, M.D., F.A.C.C., Donald A. Conetta, M.D., F.A.C.C., Theodore A. Bass, M.D., F.A.C.C., Alan B. Miller, M.D., F.A.C.C., University of Florida, College of Medicine, University Hospital, Jacksonville, FL

To understand adaptation to exercise in patients with "walk through angina" (WTA) we studied 19 patients with angiographic proven coronary artery disease. Six pat= ients with WTA and 13 control patients with typical angina (TA). We measured 2 view radionuclide angio= graphy exercise wall motion abnormalities (ExWMA), ejec= tion fraction (EF) changes, exercise heart rate, blood pressure and angina severity. (1 → 10, mild → severe). Rate pressure product (RPP) was calculated at onset of angina and at peak exercise.

Results (as mean ± S.E.M.):

	ΔRPP(10^{-3})*	ΔEF(%)*	ExWMA	Nonjeopardized Collaterals**
TA	2.1±0.8	-4.2±1.5	11/13	3/13
WTA	8.9±3.6	+5.1±2.1	6/6	5/6

*$P<0.002$ and **<0.03 WTA versus TA; ΔEF = Exercise EF - Rest EF; ΔRPP = Peak RPP - RPP at onset of angina.

In contrast to TA patients, WTA patients exercise further after onset of angina, increase their EF with exercise and have persistent ExWMA associated with com= plete resolution of their chest pain.

CONCLUSIONS: In patients with WTA: 1) Wall motion abnor= malities persist despite relief of angina symptoms. 2) Increased peak exercise ejection fraction suggests less compromise of global left ventricular function. 3) The increased presence of nonjeopardized collaterals may play a role in limiting the area of myocardium at risk.

PREOPERATIVE SUPINE EXERCISE RADIONUCLIDE ANGIOGRAM PREDICTS PERIOPERATIVE CARDIOVASCULAR EVENTS IN VASCULAR SURGERY.

S.L. Kopecky, M.D., R.J. Gibbons, M.D. FACC, L.H. Hollier, M.D. FACC, Mayo Clinic, Mayo Foundation, Rochester, MN.

To predict perioperative cardiovascular (CV) events in high risk patients (pts) undergoing peripheral vascu= lar surgery (VS), we studied 114 consecutive pts with known or suspected coronary artery disease who underwent a supine exercise radionuclide angiogram (RNA) prior to surgery. Pts with prior CABG were not included. Four pts were excluded due to inadequate RNA imaging. The exercise began at a low workload and increased until one of the following: marked ST segment depression ($\geq$ 2 mm), moderate angina, arrhythmia, or severe fatigue.

There were 8 perioperative events (7%) in the 110 pts -4 deaths and 4 myocardial infarctions (MI). The CV event group did not differ from the non event group with re= gards to age, sex, incidence of prior MI, anginal class, rest ejection fraction, change in ejection fraction or appearance of new regional wall motion abnormalities at peak exercise. However, all 8 events occurred in pts un= able to exercise over 400 kilogram-meters/minute (Kg M/M) workload.

Workload (kg M/M)	Pts.	Deaths	MI	Total Events	
$\leq$ 400	63	4	4	8	p=.01 for total events
> 400	47	0	0	0	

CONCLUSION: Peak workload, but not indices of left ventricular function, during supine exercise RNA pre= dicts a subgroup of patients with a high risk of perioperative CV events during VS.

CARDIAC OUTPUT DURING UPRIGHT EXERCISE IN CHILDREN WITH AORTIC STENOSIS

Stephen Cyran, M.D., Frederick W. James, M.D., F.A.C.C., Wayne Mays, M. Katherine Mackzum, Samuel Kaplan, M.D., F.A.C.C., Children's Hospital Medical Center, Cinti., Ohio

Few completely non-invasive and independent methods for the determination of cardiac output during exercise have been reported in children. We studied 14 consecutive patients, mean age 12±5 yrs, with isolated valvar or discrete subvalvar aortic stenosis during upright cycle ergometry. Patients rebreathed a mixture of C2H2, He, N2 and O2 at rest and peak exercise; CO was determined from a time concentration curve derived from analysis of exhaled gases. All studies were preoperative, and a cardiac catheterization was performed within 3-6 months. Oxygen consumption, heart rate (HR), and diastolic and systolic pressure were measured independently. CI, systemic vascular resistance index (SVRI) and stroke volume index (SVI) were derived. Patients were assigned to one of two groups on the basis of their resting aortic valve gradient. Results (*p<0.01)

	CO (L/min)	CI (L/min/M^2)	SVRI (+)	SVI (cc/M^2)	HR
Total					
Rest	5.3±1.7	4.2±1.1	1176±654	50±16	75±13
Exercise	12.3±4.5*	9.5±1.6*	582±359*	57±8	180±25*
Grad.<30mmHg					
Rest	5.5±1.6	4.8±1.0	1117±566	57±13	75±14
Exercise	12.2±5.4*	9.9±2.0*	643±436*	60±10	178±32*
Grad.≥30mmHg					
Rest	5.0±1.8	3.7±1.0	1235+773	42+16	75+13
Exercise	12.4±3.9*	9.0±1.1*	522±285*	59±15	182±18*

+(dynes sec/cm^5/M^2)

At rest, patients with a gradient <30 mmHg tended to have a greater CI and SVI ($p<0.07$) than those with a gradient ≥30 mmHg. These differences were abolished at peak exercise suggesting that patients with more severe aortic stenosis were able to augment their stroke volume during exercise. CI during exercise negatively correlated with SVRI (coef.-0.60,$p<0.03$) indicating that a decrease in SVR may be the causative factor.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #313/314
Doppler Echocardiographic Assessment of Diastolic Function

RELATION BETWEEN INSTANTANEOUS DOPPLER VELOCITY ACROSS THE MITRAL VALVE AND CHANGES IN LEFT VENTRICULAR VOLUME IN NORMAL, DILATED AND HYPERTROPHIED HEARTS.

Martin St.John Sutton, FACC and Ted Plappert, Brigham & Womens Hospital, Harvard Medical School, Boston, MA.

Doppler velocity (Dv) profiles across the mitral valve (MV) and Dv flow integrals have been used to assess the contributions of rapid filling (RF) and atrial systole (Asys) to LV filling, and as indicators of LV diastolic function. However the relations between changes in LV volume and instantaneous Dv have not been examined. We evaluated this relationship in 10 normals (nls) and in 18 patients (pts) with LV hypertrophy; 9 with aortic stenosis (AVS) and 9 with dilated cardiomyopathy (CM). Dv and 2D echoes (LV short and long axis) were digitized to obtain instantaneous Dv and LV volume, LV mass and LV mass/volume ratio. Peak Dv during RF in nls, AVS, and CM were similar: 62±16, 98±43, and 80±33 cm/s, but peak Dv during Asys was greatly increased in AVS 124±28 compared to CM 43±20 and nls 34±9 cm/s ($p<.01$). The percent of total LV filling achieved at these times and at the end of RF in nls, AVS, and CM were similar:

	Peak Dv (RF)	ERF	Peak Dv Asys
NL	55 ± 19	83 ± 8	98 ± 2
AS	40 ± 20	79 ± 11	93 ± 6
CM	40 ± 18	78 ± 9	92 ± 9

The magnitude of peak Dv during Asys did not reflect changes in LV volume, nor relate either to peak Dv during RF or LV mass, which was 220±38 g. in AVS and 245±29 g. in CM. Peak Dv in Asys and the ratio of peak Dv(Asys)/peakDv(RF) in the total pt population both correlated with the ratio LV mass/volume ($r=.80$, slope=.76; and $r=.80$, slope=.69), $p<.01$. We conclude that MV Dv correlates with LV architecture and not with absolute LV mass or with changes in LV volume.

LEFT VENTRICULAR DIASTOLIC FILLING DYNAMICS IN ACUTE MYOCARDIAL INFARCTION: IMMEDIATE EFFECTS OF ISCHEMIA, TIME COURSE IN FIRST 6 HOURS AND RELATION TO INFARCT SIZE.

Maxine Rosoff, M.D., FACC, John Funai, M.D., Shan Shen Wang, M.D., Natesa Pandian, M.D. Tufts-New England Medical Center, Boston, Massachusetts.

To assess the effects of acute myocardial infarction on LV diastolic filling we employed Doppler echocardiography (DE) and analyzed mitral flow velocity in 8 heart rate controlled dogs (atrial pacing), which underwent total left anterior descending coronary occlusion (CO). Mitral flow velocity (MFV) data were obtained in control (C), 5 minutes after CO and hourly for 6 hours. Pathologic infarct extent was delineated by TTC staining and size determined as %LV infarcted. From MFV, early filling velocity (E) and late filling velocity (A) were measured and E/A ratio calculated. Results: ($\bar{x}$±SE): E/A ratio in C was 1.6±0.2. Following CO, E/A ratio was: 5 min: 0.51±0.1, 1 hr: 0.74±0.2; 2 hrs: 0.75±0.3; 3 hrs: 0.74±0.3; 4 hrs: 0.45±0.2; 5 hrs: 0.47±0.2; and 6 hrs: 0.26±0.2 (All $p<.05$ compared to C). These changes were coupled with a sustained elevation in LV end-diastolic pressure from 10±1 to 16±2 mm Hg. Individually, E/A ratio fell to less than 0.8 in 7/8 dogs at 5 min of CO regardless of eventual infarct size. Infarct size ranged from 17 to 64%LV with a mean of 38±5%. In 4 dogs with infarct size >28%LV, E was totally abolished with LV filling occurring only during A during the 6 hour follow-up. Even though the E/A ratio fell significantly in the remaining dogs, there was no clear relationship between infarct size and the magnitude of change in E/A ratio. We conclude that 1) ischemia acutely impairs LV early diastolic filling irrespective of eventual infarct size, 2) filling dysfunction once established early remains abnormal for 6 hours and 3) there appears to be some but imprecise relation between the extent of filling dysfunction and infarct size.

ASSESSMENT OF DIASTOLIC LEFT VENTRICULAR FUNCTION BY DOPPLER : COMPARISON WITH CATHETERIZATION MEASUREMENTS

Niksa Drinkovic, M.D., Thomas Wisenbaugh, M.D., Oi Ling Kwan, Jonathan Elion, M.D., Mikel Smith, M.D., Anthony N. DeMaria, M.D., FACC; University of Kentucky, Lexington, Kentucky

Although measurements of LV filling velocity may be readily obtained from Doppler recordings, few data are available comparing Doppler with catheterization assessment of LV diastolic function. Therefore, we performed continuous wave Doppler examination of transmitral flow velocity in 20 patients without aortic regurgitation who underwent cardiac catheterization. At catheterization, high fidelity pressure measurements from micromanometer tip catheters were obtained simultaneously with cineangiographic LV volumes to construct pressure-volume plots during diastole. Doppler examination was performed in the 4 chamber apical view with the sample volume positioned through the center of the mitral orifice. Doppler measurements included: maximal velocity during early diastolic filling(E) and atrial contraction(A); integrated velocity of E and A diastolic filling waves; the ratio of E to A for both maximal and integrated velocities; and the time to peak early diastolic velocity (TPE). Catheterization assessment of diastolic function, included maximal negative dp/dt (an index of LV relaxation), as well as the slope of the log pressure(P)/volume(V) relationship(K) and dV/ VdP, (indices of LV passive elastance). The ratio of early and atrial filling velocities demonstrated a correlation with indices of passive elastance, with optimal correlation coefficients: r=.60 for maximal E/A vs dV/VdP and r =.68 for integrated E/.A. TPE correlated best with an index of LV diastolic relaxation: r=.81 for TPE vs negative dp/dt. Thus, these data indicate that Doppler velocity recordings may be of value in assessing LV diastolic function. Individual Doppler measurements appear to correlate best with specific diastolic properties. The optimal correlation exists between time to peak early diastolic velocity by Doppler and LV relaxation represented by maximal negative dp/dt.

DOPPLER EVALUATION OF LEFT VENTRICULAR DIASTOLIC FILLING BEFORE AND AFTER CORONARY ANGIOPLASTY Barry E. Wind, MD, A. Rebecca Snider,MD,FACC, Andrew J. Buda,MD,FACC, William W. O'Neill,MD, Eric J. Topol,MD, Univ of MI, Ann Arbor,MI

To determine if diastolic function is altered post-PTCA in patients with ischemic heart disease(IHD) and normal systolic function, 17 IHD patients and 19 normals had pulsed Doppler(Dop) exams of the LV inflow. IHD patients were examined 1 day before and 1 day after PTCA. Pre-PTCA, IHD patients had typical angina, ≥70% stenosis in 1 or 2 coronary arteries with >40 mm translesional gradient, and LV ejection fraction ≥50%. Post-PTCA, IHD patients had no recurrent angina, no residual ischemia by thallium ETT, and <40% stenosis with residual gradients < 15 mm. Dop peak velocities at rapid filling(E vel) and atrial contraction(A vel) and the ratio E/A were measured. The following Dop areas and their % of the total area(TA) were determined: 1st 33% of diastole(.33 area), and triangles under the A vel(A area) and E vel(E area). Pre-PTCA, IHD patients differed from controls(p<.01) in E vel(pre=.57±.10,NL=.68±.12 m/s), A vel(pre=.58±.13,NL=.35±.08m/s), E/A ratio(pre=1.03±.28,NL=2.03±.58), and Dop areas(table). Post-PTCA, E vel(.55±.10 m/s), A vel(.57±.12m/s), E/A ratio(1.0±.27) and Dop areas did not differ from pre-PTCA.

	E area	E area / TA	A area	A area / TA	.33 area	.33 area / TA	E area / A area
NL	.093±.019	.63±.06	.024±.006	.17±.05	.087±.02	.59±.05	4.1±1.6
PRE	.079±.016	.56±.07	.050±.015	.36±.11	.065±.02	.46±.11	1.7±.53
POST	.072±.012	.54±.09	.047±.016	.35±.11	.063±.02	.46±.09	1.7±.46

Conclusion: In patients with IHD and preserved systolic function, diastolic filling abnormalities are detectable by Dop echo. These diastolic abnormalities are unimproved 24 hours after PTCA despite angiographic, pressure gradient, thallium ETT, and clinical evidence for successful abolition of ischemia. Chronic myocardial ischemia therefore alters diastolic compliance in a manner which is not immediately reversible following relief of ischemia.

ABNORMAL PATTERNS OF LEFT VENTRICULAR FILLING IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION, ASSESSED BY DOPPLER ECHOCARDIOGRAPHY.

Eric K. Louie, M.D., F.A.C.C., Stuart Rich, M.D., F.A.C.C., Bruce Brundage, M.D., F.A.C.C., University of Illinois Hospital, Chicago, Illinois.

Patients (pts) with primary pulmonary hypertension (PPH) are thought to have intrinsically normal LV function. 2D-echo, however, shows that the ventricular septum is abnormally displaced towards the LV in systole and early diastole in these pts raising the possibility that LV filling might be altered by RV compression of the LV. To study this hypothesis, 9 pts with PPH (mean PA pressure = 61 ± 20mmHg, pulmonary vascular resistance = 18 ± 8 Wood Units) and normal pulmonary capillary wedge pressure = 6 ± 4mmHg were compared with 9 normal pts (N). LV isovolumic relaxation time (IVR) obtained from M-mode echo; ratio of late to early peak LV inflow velocity (A/E) measured by pulsed Doppler; and fractional increase in LV cavity cross-sectional area measured before and after atrial systole (Δ CSA) derived from 2D-echo short axis views at the papillary muscle level were analyzed:

	IVR (msec)	*A/E*	*Δ CSA*
PPH	*108 ± 31***	*1.7 ± 0.5***	*1.8 ± 1.3**
N	*49 ± 7*	*0.6 ± 0.2*	*0.3 ± 0.2*

***p< .001, *p <.01 for PPH vs. N*

In PPH IVR is prolonged and the inversion of the A/E ratio suggests that early inflow velocity is impeded while late inflow velocity is augmented. Correspondingly the increased ΔCSA indicates that atrial systole contributes a larger than normal proportion to LV filling. In conclusion in PPH LV filling is characterized by increased late inflow following atrial systole to compensate for impaired early diastolic filling; the latter abnormality resulting from compression of the LV by the RV in early diastole. These findings suggest that the LV in PPH may be particularly sensitive to alterations in preload and this may have important implications for vasodilator therapy.

ANALYSIS OF LEFT VENTRICULAR WALL MOTION BY PULSED DOPPLER ECHOCARDIOGRAPHY - APPLICATION TO ASSESSMENT OF MYOCARDIAL FUNCTION. Karl Isaaz, MD, Jean L. Cloez, MD, Gérard Ethevenot, MD, Nicolas Danchin, MD, Béatrice Perrot, MD, Claude Pernot, MD, FACC. Department of Cardiology, UNIV of Nancy, France.

The purpose of this study was to examine the value of pulsed Doppler Echocardiography (PDE) in assessment of left ventricular posterior wall (LVPW) motion. We studied 21 normal adult patients (pts) and 11 pts with impaired systolic LV function (angiographic systolic ejection fraction < 0,50). Two-dimensional images of the LV was obtained by placing the transducer in a standard short axis orientation and the Doppler sample volume was placed at the level of the LVPW endocardium just inferior to the mitral valve sulcus. The angle between Doppler sampling direction and direction of the mitral inflow was about 90° so that no Doppler shift frequency could be produced by the axial blood flow. The high-pass filter was set to 100 hertz so that the doppler shift frequencies of low frequency produced by the moving heart wall could be recorded. Slight adjustments in transducer angulation and sample volume position were required to maximize the audio and graphic quality of Doppler signal. The doppler waveforms was morphologically similar to the rate of change of the LVPW thickness obtained by a digitized echocardiogram, and permitted direct measurement of maximal LVPW velocities during systole and diastole. In normal pts, the maximal LVPW velocity ranged from 7.1 to 11.5cm/s (mean 8.7±1.1) in systole, and ranged from 13.2 to 24.3 cm/s (mean 19.5 ± 2.9) in diastole. By contrast, the average values for the 11 pts with impaired systolic LV function was depressed to 5.7±0.9cm/s in systole (p<0.01). We conclude that PDE may be used for analysis of instantaneous LVPW velocities, providing a new method for assessment of LV function.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #264/265/266
Intra-operative Doppler Echocardiography

INTRAOPERATIVE ASSESSMENT OF MITRAL VALVE REGURGITATION BY TRANSESOPHAGEAL DOPPLER ECHOCARDIOGRAPHY
Bruce Shively, M.D., Michael Cahalan, M.D., David Benefiel M.D., Nelson Schiller, M.D., F.A.C.C.

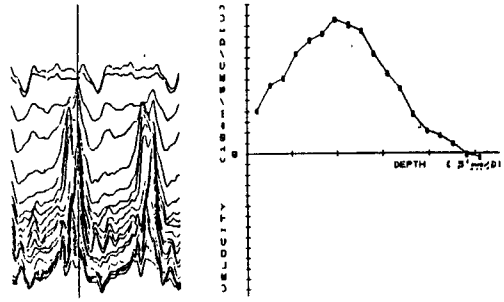
In patients (pts) undergoing mitral valve surgery, a method for the intraoperative evaluation of mitral valve function just prior to and immediately following cardiopulmonary bypass would be clinically useful. We assessed the value of intraoperative transesophageal Doppler echocardiography in six pts undergoing mitral valve valvuloplasty (MVplasty) or replacement (MVR). Two pts had rheumatic mitral stenosis (MS), two pts had mitral regurgitation (MR) due to mitral valve prolapse (MVP) and two pts had bioprosthetic malfunction. In pts with MS the presence and severity of MR was assessed intraoperatively by Doppler to guide the surgical decision between commissurotomy versus valve replacement. In the two pts with MVP-MR, posterior MVplasty with Duran ring implant was performed. In these, the adequacy of repair was assessed intraoperatively by the absence of demonstrable MR as the pts were weaned from cardiopulmonary bypass. The decision to defer valve replacement was based partially on these studies. Similarly, in the four pts undergoing MVR, normal prosthetic function (no significant MS or MR) was shown intraoperatively. Follow-up precordial Doppler echocardiography on all six pts showed no MR in three pts and slight MR in three others. In conclusion, this technique appears to have value in the intraoperative assessment of the results of mitral valve surgery. The sensitivity of transesophageal Doppler echocardiography in the detection of MR is comparable to that of the precordial technique. The limitation on transducer positioning intrinsic to the transesophageal approach may present difficulty in the detection of small eccentrically-directed mitral regurgitant jets.

DOPPLER ECHOCARDIOGRAPHIC MEASUREMENT OF CARDIAC OUTPUT USING AN IMPLANTABLE AORTIC TRANSDUCER.
William J. Stewart, M.D., F.A.C.C., William A. Schiavone, D.O., F.A.C.C., Ernesto E. Salcedo, M.D., F.A.C.C., Paul Rom, Altagracia M. Chavez, M.D., Delos M. Cosgrove, M.D., F.A.C.C.

Cardiac output in post-operative cardiac surgery pts has traditionally been measured using thermodilution techniques (TDCO). In other settings, Doppler echocardiography has been used to calculate cardiac output (DCO) using the product of the cross-sectional area (CSA) of the aorta, the mean velocity (V) derived from the Doppler signal, and the heart rate. We studied 11 patients with a miniature Doppler probe implanted in the ascending aortic adventitia. CSA was derived from direct caliper measurement of aortic diameter. Postoperatively, V was measured by D in order to calculate cardiac output continuously. Simultaneous TDCO and DCO were compared at baseline, after volume loading, during Dopamine infusion, and during atrial pacing. The Doppler transducer was removed within 24 hours with no complications. Results: In 7 of the 11 pts, DCO correlated significantly with TDCO (r values ranged from .57 to .92). Of 4 pts in whom DCO did not correlate significantly with TDCO, 2 had aortic prostheses and in one, a obvious change in the V signal indicated a shift in transducer position. In 4 pts, a CSA setting other than that measured by calipers was needed to make the volumetric flow similar to the TDCO measurement. Reproducibility of DCO (r = .98) was superior to TDCO (r = .91). Conclusions: 1) DCO measurement using an implantable probe is a safe and promising technique which needs further refinement; 2) DCO measures relative changes in flow adequately; however, accurate measurement of absolute volumetric flow is limited by inaccuracies in CSA measurement 3) DCO gives reproducible minute-to-minute flow data, without the repeated injections or nursing attention required for TDCO.

ANALYSIS OF FLOW VELOCITY PROFILE AT THE AORTIC ROOT MEASURED WITH ULTRASONIC PULSED DOPPLER TECHNIQUE.
Megumi Mathison, M.D., Hiroshi Matsumoto, M.D., Ph.D., Ken-ichi Asano, M.D., Ph.D., Univ of Tokyo, Tokyo, JAPAN.

Although it has been believed that the flow velocity profile at the aortic root is uniform like a trapezoid, our recent study about aortic valve calcification suggested that somewhat jet-like flow velocity distribution might exist at the aortic root. To analyze the distribution of flow velocity at the aortic root, special apparatus using ultrasonic pulsed doppler, connected to the computer and the display, with the direct probe on the aortic wall was designed. The flow velocity profiles were described by the three-dimentional graph. Six patients were examined when they underwent the open heart surgeries, none of 6 subjects were related to the aortic valve diseases; three with ASD, two with coronary artery disease, one with mitral valve disease. Jet-like flow patterns were always found and it was also shown that the jet was not in the center, but obliquely toward the right. In conclusion, in this study we have demonstrated the jet formation at the aortic valve.



INTRAOPERATIVE DOPPLER MEASUREMENT OF MITRAL REGURGITANT FLOW VELOCITY - COMPARISON WITH THE SYSTOLIC LEFT VENTRICULAR TO LEFT ATRIAL PRESSURE GRADIENT.
William J. Stewart, M.D., F.A.C.C., William A. Schiavone, D.O., F.A.C.C., Ernesto E. Salcedo, M.D., F.A.C.C., Andrew Benko, B.S.E.T. Carl C. Gill, M.D., F.A.C.C., Bruce W. Lytle, M.D., F.A.C.C., Delos M. Cosgrove, M.D., F.A.C.C. The Cleveland Clinic Foundation, Cleveland, Ohio.

Previous studies of Doppler (D) echocardiography in tricuspid regurgitation and in pts with stenosis of the aortic, mitral, pulmonic, and tricuspid valves, show that the D estimation of gradient (G-DOP) correlates well with invasively measured pressure gradient (G). To evaluate if G-DOP also correlates with the systolic left ventricular to left atrial pressure gradient (G) in mitral regurgitation (MR), we measured MR velocity (V) intraoperatively in 13 patients using sterile D transducers placed directly on the heart. G was measured simultaneously using direct puncture of the LV and LA and solid state hub transducers. G-DOP was calculated using the Bernoulli equation (G-DOP = $4V^2$).
Results: In 10 pts G-DOP varied from 41 to 159 (mean 84.4) mm Hg, while G varied from 54 to 163 (mean 84.2) mm Hg; the mean difference between G and G-DOP was only 10.6 $\pm$ 9.7 (range 0 to 31) mm Hg. The shape of the V envelope reflects the algebraic difference between LA and LV pressure. In 3 pts with flail mitral valves, D signals did not show a clean envelope despite the advantages of intraoperative access.
Conclusions: The Bernoulli equation appears to govern the relationship between V and G in MR, similar to the physics present in valvular stenosis. This allows a better understanding of the V patterns seen in MR. However, D recordings of V in MR are not presently accurate enough to derive LV filling pressures noninvasively.

THE COLOR CODED MULTIGATE M-MODE DOPPLER DISPLAY IN A REAL-TIME FLOW MAPPING SYSTEM: DOES IT PROVIDE ADDITIONAL INFORMATION? Richard E. Swensson,M.D.,F.A.C.C., David J. Sahn, M.D.,F.A.C.C., Lilliam M. Valdes-Cruz, M.D., F.A.C.C., Kyung J. Chung, M.D., F.A.C.C., Frederick S. Sherman, M.D., Univ of Calif, San Diego, CA.
We examined the information content of the color coded multigate Doppler M-Mode or MQ display obtained along with 2D flow mapping and single-gate spectral Doppler in 14 patients(PTS) with ventricular septal defects(VSD), 7 PTS with patent ductus arteriosus(PDA), and 4 open chest dogs with a variable sized AO to PA "PDA-like" shunt. In the VSD PTS at heart rates >100/min, the 15 frame/sec rate of the 2D flow map made it difficult to appreciate in real-time, bidirectional shunting, present at catheterization in 5. Single-gated spectral Doppler demonstrated the bidirectional shunt in only 4 PTS, even when sampling under 2D flow imaging guidance. The MQ display by showing flow direction proximal and distal to the position of the single gate gave additional information as to the timing of formation of both left-to-right and right-to-left shunt jets and their penetration across the septum. In the 7 PDA PTS and in the animal model of variable PDA, we found that the 2D flow map localized the ductal shunting stream but that the MQ display showed more accurately the phasic timing of its penetration into the PA towards the pulmonary valve. In small PDA shunts the MQ mode showed that especially in systole, the ductal shunt was sequestered in the distal PA by forward flow and was directed into the left PA so that it did not penetrate the main PA or appear on the main PA sampled spectral Doppler. The real-time flow map, single-gate spectral and MQ modes of Doppler display each have a unique information content. The MQ display has the advantage of a fast multigate sampling rate to aid delineation of cardiac physiology, especially in shunt lesions.

HOW SENSITIVE IS STRESS DOPPLER ECHOCARDIOGRAPHY IN THE DETECTION OF TRANSIENT ISCHEMIA IN CORONARY STENOSIS?
Morgan Werner MD, John Funai MD, Shan Shen Wang MD, Natesa Pandian MD. Tufts-New Engl. Med. Ctr., Boston, MA.

Our aim was to assess the effects of transient stress-induced ischemia on aortic flow velocity (AFV) in the setting of coronary stenosis. To do this we studied 5 dogs in which experimental one or two vessel coronary stenoses were created using a calibrated occluder. Atrial pacing stress was employed and 20 instances of ischemia were produced. Presence of ischemia was verified by the development of LV wall dysynergy detected by 2D echo. Using Doppler echocardiography (DE) we recorded the AFV in the dogs with coronary stenosis during resting state without ischemia and again immediately after development of stress induced ischemia. From the aortic flow profile we measured peak velocity (PV) and acceleration rate (AR). A wall motion score was computed incorporating both the spatial extent and the magnitude of LV dysynergy. A wall motion score less than 70 indicated mild dysynergy; 70-120=moderate LV dysynergy and greater than 120=severe dysynergy. Results: ($\bar{x}$±SD). PV was 0.8±.18 m/s in resting coronary stenosis and 0.79±.16 during stress ischemia (p=NS). PV increased during 8 ischemic episodes, showed no change during 2 and fell during 12 episodes. AR was 13.04±4 m/s^2 during resting coronary stenosis and 11.2±4 m/sec^2 during stress ischemia (p<.01). AR fell during all but 3 of the 20 instances of ischemia. AR always fell whenever the wall motion score exceeded 70. We conclude that: 1) measurement of aortic peak velocity is not sensitive in detecting transient myocardial ischemia, 2) a decrease in aortic flow velocity acceleration rate is a sensitive indicator of transient ischemia in coronary stenosis only when there is significant LV dysynergy. These findings indicate a need for caution in the use of stress Doppler echocardiography.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #264/265/266
Anti-Ischemic Drug Therapy

ISOSORBIDE 5 MONONITRATE AS MONOTHERAPY IN PATIENTS WITH CHRONIC STABLE ANGINA
Fawaz Akhras, MD, Graham Jackson, FRCP. Cardiac Department, King's College Hospital, London, England UK

Isosorbide-5-mononitrate (ISMN) is not subject to first pass metabolism. To evaluate its efficacy as monotherapy in patients with chronic stable angina 14 patients with coronary artery disease were studied. All were limited by angina on a treadmill exercise test. After a 2-week placebo period ISMN was administered in a single blind fashion titrating the dosage at 2 week intervals. The increments were 20 mg once daily, 20 mg twice daily, 40 mg once daily and 40 mg twice daily. Patients were assessed subjectively by anginal attack rate and glyceryl trinitrate (GTN) consumption and objectively by treadmill exercise testing at 12 hours post dosage. ISMN increased the exercise ability significantly from 319 ± 21 (SE) secs on placebo to 394 ± 26 ($p < 0.001$) on 20 mg once daily to 434 ± 27 ($p < 0.001$) on 20 mg twice daily to 445 ± 26 ($p < 0.001$) on 40 mg once daily and to 465 ± 27 ($p < 0.001$) on 40 mg twice daiy, increases of 24, 36, 39 and 46% respectively. However, a significant reduction in ST segment depression occurred only with the twice daily regimes. This objective improvement was associated with a significant decrease in anginal attacks from 21.4 ± 5.7 on placebo to 11.3 ± 4.5 ($p < 0.001$) on 20 mg twice daily, to 10.9 ± 4.6 ($p<0.001$) on 40 mg once daily and 7.1 ± 3.0 ($p<0.001$) on 40 mg twice daily, a reduction of 48% 50% and 67% respectively. GTN consumption decreased similarly. ISMN is an effective antianginal agent with no signs of early tolerance. Whilst no significant difference emerged between 20 and 40 mg twice daily individual variations occurred, indicating a need for dosage flexibility.

NICARDIPINE INCREASES MYOCARDIAL CONTRACTILITY AND REDUCES PACING INDUCED ISCHEMIA.
Martin A. Josephson, M.D., F.A.C.C., Kristine Coyle, B.A., Barbara Behnke, R.N., Bramah N. Singh, M.D., Ph.D., F.A.C.C., Wadsworth VA Medical Center, Los Angeles, CA.

The hemodynamic and anti-ischemic effects of nicardipine(N), a new dihydropyridine calcium antagonist, are poorly defined. Therefore, 17 patients with coronary artery disease(CAD) undergoing catheterization were given N 2mg bolus followed by a 6 mg infusion over 30 min. producing a mean serum N of 147 ± 30 ng/ml. Standard hemodynamic variables, radionuclide left ventricular ejection fraction(LVEF), and thermodilution coronary sinus flow(CSF) were measured at rest and during pacing-induced ischemia before and after N. Results:Means ±SD:

	Control vs N	Pacing vs Pacing+N
HR(beats/min)	71±13 79±14**	129±14 129±14
AO(mmHg)	107±14 85±9 **	124±18 94±11**
PCW(mmHg)	9±4 8±3	15±5 10±4**
PA(mmHg)	15±3 16±4	21±4 18±3**
RA(mmHg)	8±3 8±2	9±3 8±3
CI(L/min/M^2)	2.2±.3 2.8±.4**	2.6±.5 3.2±.5**
LVdp/dt	1509±376 1660±465 (n=8)	
CSF(ml/min)	105±58 154±88**	188±117 169±67
MVO_2(ml/min)	10±5 9±5	21±13 14±6*
LVEF(%)	57±9 68±7**	48±12 63±10**

(*p<0.05 **p<0.01 Comparison between control and N, and between Pacing and Pacing+N).

N reduced systemic and coronary resistance before (39%; 46%) and after (39%; 14%) pacing. N also decreased pacing-induced angina and improved % myocardial lactate extraction during pacing from -15.7 to -4.7. Conclusions: 1) N is a coronary and systemic vasodilator which causes increases in CI, CSF, and LVEF. 2) N lessens the ischemia-induced fall in LVEF and the increase in PCW. 3) The absence of a negative inotropic effect and the hemodynamic profile of N are favorable for treatment of patients with coronary artery disease and suggest N may be useful in CAD patients with impaired LVEF.

BENEFICIAL CLINICAL AND HEMODYNAMIC EFFECTS OF LABETALOL IN ISCHEMIC HEART DISEASE
Xavier E. Prida, M.D., Robert L. Feldman, M.D., F.A.C.C., James A. Hill, M.D., F.A.C.C., Carl J. Pepine, M.D., F.A.C.C., University of Florida, Gainesville, Fl.

Coronary and systemic hemodynamic effects of Labetalol (L), a nonselective beta adrenergic blocker with the ancillary property of alpha 1-adrenergic blockade were investigated at rest and during supine bicycle exercise in 12 normotensive patients (pts).

Before L, exercise evoked angina in all pts. After L (IV, 0.5 mg/kg) at the same Ex work load which evoked angina before L, angina occurred in only 4 pts. No adverse effects occurred after L.

At rest, L reduced mean AoP, (100±12,mean±SD to 92±9 mmHg, p<.05), as cardiac output, CO (7.1±1.2 to 7.9±1.8 L/min,p<.05) increased and CSF, (133±45 to 137±35 ml/min, p=NS) was preserved without an increase in HR (70±11 to 68±8 b/min, p=NS). During exercise CO (11.3±2.6 to 10.1±2.4 L/min, p=NS) and CSF (225±62 to 180±62 ml/min, p=NS) were only slightly lower after L than during control exercise while mean AoP (118±14 to 104±9 mmHg, p<.05) and HR (100±13 to 88±7 b/min,p<.05) were reduced. The relationship between CO and LVEDP improved at rest after L and improvement was maintained during exercise. LVdp/dt max. however, decreased slightly at rest (1602±282 to 1476±250 mmHg/sec) and during peak exercise (2288±775 to 1803±569 mmHg/sec) after L (both p<.05).

Thus, L has a unique hemodynamic profile among drugs which produce beta blockade. L combines vasodilator and beta blocker actions resulting in beneficial hemodynamic effects in normotensive pts with CAD.

IMPACT OF SUBLINGUAL NITROGLYCERIN ON THE CORONARY COLLATERAL CIRCULATION IN MAN.

John W. Danforth, M.D., Thomas A. Ports, M.D., F.A.C.C., Elias H. Botvinick, M.D., F.A.C.C., Michael Dae, M.D., J. William O'Connell, M.A., William W. Parmley, M.D., F.A.C.C., University of California, San Francisco.

Nitroglycerin (NTG) has been shown to enhance coronary collateral blood flow within regions of myocardial ischemia in animal experiments. To determine the impact of NTG on myocardial collateral circulation in man, during transient ischemia, selective intracoronary injection of radio-labeled MAA particles (15-40u) was performed in 11 pts during angioplasty balloon dilatation and occlusion of the contralateral diseased coronary artery before & after the administration of sl NTG. A log transform color enhanced computer comparison of the scintigraphic images obtained before (A) & after (B) NTG was used to detect the effect of NTG on collateral distribution. Relative to the native coronary distribution, NTG resulted in a modest increase in the region of anticipated collaterals (11±12% in LAO 45, 6±7% in ANT) in 9 of 11 pts. In 2 pts, NTG resulted in a reduction in collateral distribution. Although the mean BP fell in all pts $\bar{p}$ NTG ($p=.01$), the mean BP of these 2 pts (72±5 mm Hg) was lower than the mean BP of the other 9 pts (84±9 mm Hg) $\bar{p}$ NTG. Relative to the distribution of the collaterals, (determined in 4 pts by comparing (A) to the distribution of MAA injected $\bar{p}$ PTCA), NTG resulted in a substantial increase in collateral distribution (range: 10-210% in LAO 45°, 29-85% in ANT). These data suggest that sl NTG enhances the distribution of coronary collateral blood flow in man during transient ischemia provided that the mean BP is maintained. That NTG enhanced collateral distribution despite a consistent reduction in mean BP suggests that NTG effects vasodilatation of coronary microcollaterals.

THE EFFECT OF INTRACORONARY NITROGLYCERIN ON MYOCARDIAL BLOOD FLOW TO CORONARY COLLATERAL-DEPENDENT REGIONS.

John T. Miller, MD, Rodney L. Henry, MD, Morton J. Kern, MD, FACC, Robert A. O'Rourke, MD, FACC. University of Texas Health Science Center, San Antonio, TX.

Intracoronary (IC) nitroglycerin (NTG) augments myocardial blood flow (MBF) to regions perfused by normal as well as partially occluded coronary arteries (CA). The effect of IC NTG on collateral MBF to areas of infarcted myocardium is less well known. Such patients(pts) often undergo procedures during which IC NTG is administered. Therefore, to determine the effects of IC NTG on MBF to collateral dependent regions, we measured heart rate(HR), mean arterial pressure (MAP), great cardiac vein blood flow (GVF) by continuous thermodilution technique during a 200 mcg bolus of IC NTG. Great vein resistance (GVR)=MAP ÷ GVF. Group (Gp) I pts had normal CA. Gp II pts had >70% narrowing of the left anterior descending (LAD) CA. Gp III pts had total occlusion of the LAD, anterior wall dysynergy and the LAD was supplied by angiographic collateral CA. There was no significant change in HR or MAP during IC NTG. Peak (pk) GVF, change (Δ) in GVF and percent (%) Δ as mean ± SD during IC NTG were:

	GpI(n=6)	GpII(n=9)	GpIII(n=7)
pk GVF(ml/min)	140±60	86±27*	76±40*
ΔGVF	65±41	28±15*	14±15**
%ΔGVF	84±38	50±31	19±18+**

*p<.05 **p<.01 GpI vs.GpII or III +p<.05 GpII vs.GpIII The ΔGVR & %ΔGVR paralleled pk GVF. Conclusion: The MBF response to IC NTG is preserved but significantly attenuated in infarcted regions supplied by collateral CA; however, because IC NTG significantly increased MBF from control in all Gps, IC NTG may relieve ischemia during invasive procedures likely to alter MBF to collaterally-dependent regions.

BEPRIDIL VERSUS NIFEDIPINE FOR TREATMENT OF CHRONIC STABLE ANGINA.

Richard J. Katz, M.D., F.A.C.C., Udho Thadani, M.D., F.A.C.C., and the Bepridil-Nifedipine Multicenter Study Group, George Washington University, Washington, DC.

Bepridil (B), a new once-a-day calcium blocker, has been shown to be an effective antianginal drug. We compared B to nifedipine (N) in 97 pts with chronic stable angina (≥5 anginal attacks/week) and abnormal treadmill exercise test (TET) (≥1 mm ST depression with chest pain). Protocol was parallel design consisting of a 2 week single-blind placebo phase and a 7 week double-blind dose titration phase to maximum tolerated dose. Dose range for B was 200-400 mg/day (270±55mg) and for N 30-120 mg/day (53±21mg). Patients were evaluated with TET and diaries in each phase. Baseline treadmill and clinical findings were similar in both groups. Results are expressed as change (Δ) from placebo to drug for each parameter (total treadmill time = TT; time to angina = TA; time to 1 mm ST depression = TST; angina frequency/week = A/wk; nitro usage = NTG/wk).

	ΔTT(min)	ΔTA(min)	ΔTST(min)	ΔA/wk	ΔNTG/wk
B	1.2±1.7	2.1±2.3	1.4±2.1	-7.9±8.1	-4.1±14.3
N	0.4±1.8	1.3±1.8	0.2±2.6	-3.9±6.8	-2.9± 6.5
p(BvsN)	.05	.07	.03	.02	NS

Additionally, resting heart rate decreased on B (72.9±→65.2±/min) and increased on N (70.8±→73.0±/min), $p<.001$. QTc increased on B (.41→.44±/msec) and was unchanged on N (.40±→.41±/msec), $p<.03$. Adverse reactions requiring drug discontinuation were noted in 4/49 (8%) pts on B versus 12/48 (25%) on N ($p<.05$). Conclusions: Comparing B to N, B provides better anginal relief and somewhat enhanced treadmill performance with fewer side effect related to drop outs.

Thursday, March 13, 1986
8:30AM-10:00AM, Room #260/261
Exercise Testing

SIGNIFICANCE OF EXERCISE-INDUCED T WAVE NORMALIZATION IN THE ECG DURING TREADMILL TESTING

Jairo Marin MD, Ming K. Heng MD FACC, Roger Sevrin MD, Vasant N. Udhoji MD FACC, Sepulveda VA Medical Center and UCLA School of Medicine, Los Angeles, CA.

Normalization of previously inverted T waves is often noted during exercise treadmill testing (ETT) but has been of uncertain significance. To study this, we reviewed 578 thallium-ETT and found T wave normalization during or immediately after exercise in 35 men (ages 37-77 yr, mean 59). ETT was done using the Bruce protocol with 2.2 mCi of thallium-201 (T-201) injected 1 minute before the end of exercise. Computarized T-201 images were obtained in standard projections immediately after exercise and 4 hours later. ECG and T-201 imaging were analyzed with regard to changes in the anterior-septal (AS) and inferior-posterior (IP) cardiac segments. 34 of 35 patients had positive T-201 imaging consistent with previous infarction or exercise-induced ischemia. 97% (64/66) of segments with T wave normalization were associated with positive T-201 imaging. 95% (21/22) of segments with T wave normalization in IP leads, and 97% (43/44) of segments with T wave normalization in AS leads, had positive T-201 imaging. Of 21 segments with IP T wave normalization, 71% (15/21) had positive T-201 imaging in IP sites. Of 44 segments with AS T wave normalization, 73% (32/44) had positive T-201 imaging in AS sites. For segments with previous infarction, the site correlation was 80% (28/35) for AS segments, and 70% for IP segments. For segments showing exercise ischemia, the site correlation was 75% (9/12) for AS segments, and 70% (7/10) for IP segments. Conclusion: T wave normalization during ETT indicates presence of coronary artery disease in over 95% of instances. It localizes the affected site in about 70% of cardiac segments, suggesting that it represents mainly a primary, rather than reciprocal, ECG change.

HEART RATE ADJUSTED ST SEGMENTS VERSUS THALLIUM SCINTIGRAPHY IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE

Robert Detrano, M.D., and Ernesto E. Salcedo, M.D., F.A.C.C. Cleveland Clinic Foundation, Cleveland, OH.

Heart rate adjustment of stress induced ST depressions has shown good correlation with the results of coronary angiography (CA), but there have been no comparisons of heart rate (HR) adjustment with thallium scintigraphy (T). We submitted 303 consecutive subjects (206 men, mean age 54 years) without prior myocardial infarction referred for CA to exercise EKG (XEKG) and T. Fifty-five percent had at least 1 >50% CA obstruction. Unadjusted and adjusted ST segment depressions (mm/beats/min) and T defects were compared with the results of CA (>50% obstruction):

	ST depression 1 mm	HR adjusted ST 0.015	T
Cutpoint			
Specificity	73%	79%	79%
Sensitivity	65%	66%	73%
Accuracy	70%	73%	76%

Comparing XEKG with the results of T (any perfusion defect):

	ST depression 1 mm	HR adjusted ST 0.013
Cutpoint		
Specificity	67%	67%
Sensitivity	59%	61%
Accuracy	63%	64%

We conclude that HR adjustment of XEKG improves accuracy compared to CA, but not to T, and is inferior to T when both are compared to CA.

DETERMINANTS OF THE HEMODYNAMIC EFFECTS OF ISOLATED PROXIMAL CORONARY STENOTIC LESIONS ON REGIONAL MYOCARDIAL PERFUSION DURING EXERCISE

Allen B. Nichols, MD, FACC, Thomas A. Schwann, BA, Jennifer Han, BA, Peter Esser, PhD, and David K. Blood, MD, FACC. Columbia University, New York, NY

This study tested the hypothesis that absolute dimensions of coronary stenotic lesions are more important determinants of their hemodynamic effect on regional myocardial perfusion during exercise than percent relative stenosis. The 22 patients studied had isolated proximal lesions of the left anterior descending artery (LAD) without prior myocardial infarction. Regional myocardial perfusion was assessed from quantitative thallium-201 scans obtained in the left anterior oblique projection after symptom-limited treadmill exercise. The minimal cross-sectional area (mm^2), diameter (mm), and percent area reduction of LAD stenoses was measured by computer-assisted cinevideodensitometric analysis of projected coronary arteriograms digitized in a 512x512 pixel matrix with 256 grey levels. Tl-201 uptake in the LAD distribution, expressed as a ratio of Tl-201 in the circumflex (CX) distribution, correlated poorly (r=-0.66) with relative percent stenosis. However, LAD/CX ratios correlated well with absolute lesion area (r=0.83) and with lesion diameter (r=0.84). Thus, execise-induced Tl-201 perfusion defects correlate best with absolute dimensions of coronary stenotic lesions. Relative coronary stenosis, expressed as a percentage, is a less precise predictor of the hemodynamic effects of a stenotic lesion, which is consistent with principles of fluid mechanics.

ARM EXERCISE THALLIUM TESTING: A RELIABLE METHOD FOR DETECTING CORONARY DISEASE.

Gary J. Balady, M.D., Donald A. Weiner, M.D., F.A.C.C., James A. Rothendler, M.D., F.A.C.C., Cindy Mangene, B.S., John LaGambina, A.S., Charles McCarthy, A.S., and Thomas J. Ryan, M.D., F.A.C.C., Boston University Medical Center, Boston, Massachusetts.

Patients with lower extremity impairment are often unable to perform standard exercise tests (ET). To assess the diagnostic accuracy of thallium scintigraphy during upright arm ergometry ET, we studied 50 patients (age 56 ± 10 years) prior to cardiac catheterization for evaluation of coronary artery disease (CAD). Significant CAD (≥70% stenosis) was present in 41 patients (82%). Exercise was begun at 10 watts and continued at 10 watt increments every 2 minutes. The test was terminated for moderate angina in 5 (10%), marked ST depression (>3 mm) in 1 (2%), and fatigue in 44 patients (88%). All thallium images were of diagnostic quality and read independantly according to a qualitative scoring system by 2 observers blinded to clinical and angiographic data. Electrocardiograms (ECG) were blindly analyzed for ≥1 mm ST depression. Results were as follows:

	Sensitivity	Specificity	Predictive Value Positive	Predictive Value Negative
Thallium	83%*	78%	94%	50%
ECG	54%	67%	88%	24%

*p<0.01

We conclude that thallium scintigraphy during arm ET is: 1) more sensitive and specific, and has a better predictive value for the diagnosis of CAD than the ECG response alone; and 2) is a practical alternative test for evaluating CAD in patients with lower extremity impairment.

PROGNOSTIC STRATIFICATION BY THALLIUM SCINTIGRAPHY: WHO NEEDS IT?

Todd S. Kotler, M.D., Brad H. Pollock, MPH, Jeffery W. Work, M.D., George A. Diamond, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, CA.

Does thallium scintigraphy improve the prognostic assessment of patients already stratified according to disease probability? Disease probability (P) was calculated by Bayesian analysis of age, sex, symptoms, exercise duration and ST segment response in 1370 patients without prior infarction. Patients were then grouped into low (P<0.1), intermediate (0.1<P<0.9) and high (P>0.9) disease probability groups. Thallium scintigrams were interpreted as negative, equivocal or positive. There were 35 coronary events (cardiac death or nonfatal infarction) in the year following testing. This overall event rate of 2.6%, however, ranged from a low of 0.6% in the 159 patients with low probability and a negative scintigram to 8.8% in the 227 patients with high probability and a positive scintigram:

THALLIUM	CORONARY EVENTS (%) P<0.1	0.1<P<0.9	P>0.9	TOTAL
NEG	1/159 (0.6)	4/277 (1.4)	2/184 (1.1)	7/620 (1.1)
EQUIV	1/72 (1.4)	1/155 (0.6)	1/114 (0.9)	3/341 (0.9)
POS	0/58 (0.0)	5/124 (4.0)	20/227 (8.8)	25/409 (6.1)
TOTAL	2/289 (0.7)	10/556 (1.8)	23/525 (4.4)	35/1370 (2.6)

Thus, scintigraphy allowed an eightfold improvement in prognostic risk stratification in the 525 high probability patients (p<0.0001) and a threefold improvement in the 556 intermediate probability patients (p=0.05). Stratification in the low probability subset was not improved (p=0.7). We conclude that testing is capable of providing important prognostic information even when this information is redundant relative to diagnosis.

EXERCISE TESTING AND THALLIUM SCINTIGRAPHY FOR THE DIAGNOSIS OF CORONARY DISEASE: AN OPTIMAL COST-EFFECTIVE STRATEGY

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We have shown that the diagnostic value of maximal(max) exercise(ex) was greatly enhanced by a multivariate and compartmental analysis(MEX)(Eur.H.J.,6,277,1985). Since thallium ex scintigraphy is also used for diagnosis of CAD, we have compared these 2 methods in 277 men without myocardial infarction who all underwent bicycle MEX and TL; coronary arteriography (CA) was the diagnostic standard. The ex ECG was averaged by computer; 5 ex variables were selected by multivariate analysis of the data collected at peak ex(heart rate,ST level,angina at max ex, max workload and ST segment slope); the results of this analysis were entered in a compartmental and bayesian model.TL data was visually analyzed (normal(nl) or abnormal(anl)).

From history, the pre-test likelihood(L) of CAD was calculated from the available tables; the post-test(POST) L was calculated from Bayes formula after 4 diagnostic strategies: (1)MEX only; (2)TL only; (3)MEX and TL in all patients(pts) and (4)MEX in all pts and TL only in pts with a diagnostic uncertainty after MEX(10%<POST<90%). The average information content ($\bar{I}$) was calculated after each strategy as well as the accuracy of the classification of the pts: correct=POST>90% with anl CA or <10% with nl CA, incorrect=POST<10% with anl CA or >90% with nl CA, uncertain in other situations.

The $\bar{I}$ and the classifications are given in the table:

STRATEGY	$\bar{I}$	correct	uncertain	incorrect	Mc Nemar
(1)	39%	76%	18%	5%	] 0.001
(2)	36%	68%	30%	2%	] 0.001
(3)	57%	81%	15%	4%	] 0.003
(4)	-	83%	10%	6%	

Thus, the diagnostic value of MEX is slightly superior to that one of TL since it provided a greater $\bar{I}$. The best classification of the pts was provided by strategy (4). This strategy using sequential testing is cost-effective since it allowed to avoid TL in 81% of the pts without loss of accuracy. The incorrectly classified pts after strategy (4) included only 5 CAD pts who had all a single vessel disease.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #260/261
Cardiac Function and Exercise

STRATIFICATION OF SUBMAXIMAL AND MAXIMAL EXERCISE RESPONSE ACCORDING TO FUNCTIONAL CLASS IN PATIENTS WITH CONGESTIVE HEART FAILURE.

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Submaximal (sm) and maximal (max) exercise (Ex) was compared in 21 patients (pts) with congestive heart failure. LV ejection fraction was <20% in all pts. Maximum oxygen uptake (MVO_2, ml/kg/min), HR (beats/min), skeletal muscle blood flow (MBF, ml/min) using xenon^{133}, and femoral vein oxygen saturation (FVO_2, ml/100ml), lactate and ph (FVph) were measured throughout treadmill Ex at max (100% MVO_2) and sm (50-70% MVO_2) workloads, and were as follows:

	Class IV n=5		Class III n=6		Class II n=5		Class I n=5	
	sm	max	sm	max	sm	max	sm	max
VO_2	8.4	9.8	8.6	13.8	10.9	17.7	13.7	22.5
FVO_2	31	28	32	28.5	33	29	29	27
FVph	7.26	7.23	7.35	7.30	7.39	7.27	7.39	7.27
HR	135	140	118	135	109	143	100	144
$\frac{max}{sm}$ MBF	0.86		1.1		2.1		7.6	

During max Ex, a linear rise in FV lactate over time was documented in all pts. With sm Ex, pts in Class I-III displayed an early rise with subsequent plateau in lactate concentration for the remainder of Ex. However, pts with Class IV had a continual increase in lactate concentration over time even at the lowest sm workloads. Thus, 1) pts with Class I have preserved Ex performance due to their ability to vasodilate; 2) sm Ex is sufficient to elicit max MBF in pts with Class III-IV; 3) the continual rise in lactate production in pts with Class IV invalidates the concept of anerobic threshold and sm Ex levels in this group.

ALTERED RENIN-ANGIOTENSIN-ALDOSTERONE ACTIVATION DURING EXERCISE INDUCED BY CHRONIC ACE INHIBITION IN HEART FAILURE

Philip C. Kirlin, M.D., F.A.C.C., Carolyn Koestner, R.N., Park W. Willis, III, M.D., F.A.C.C., Cardiology Section, Michigan State University, East Lansing.

Heart failure (CHF) often activates the renin-angiotensin-aldosterone system (RAAS), resulting in increased plasma renin activity (PRA) and increased plasma aldosterone (aldo) levels. Exercise (E) in CHF and angiotensin converting enzyme inhibition (ACEI) further elevate PRA. In order to assess the effects of chronic ACEI on RAAS activation during E in CHF, NYHA Functional Class 2-3(n=8) or 4(n=1) patients receiving digitalis and diuretics performed maximum treadmill E before and after 8-12 wk lisinopril (10-15 mg/d) or captopril (25-50 mg tid). Before ACEI, E caused elevated PRA (rest to E, 5.5±1.7 to 7.4±2 ng/ml/h, $p<.04$, ±SEM). However, plasma aldo did not change with E (376±96 to 381±94 pg/ml $p>.9$). As expected, chronic ACEI elevated PRA at rest (to 18±1.3 ng/ml/h) and decreased plasma aldo at rest (to 160±21 pg/ml). At the same level of E as before ACEI, PRA rose even higher during chronic ACEI (to 20.4±1.3, $p<.01$). However, with chronic ACEI plasma aldo also rose during E (to 190±28, $p<.04$). These data indicate: 1. Converting enzyme blockade is sustained during chronic (8-12 wk) ACEI in CHF (elevated PRA and decreased plasma aldo). 2. E induced PRA elevations in CHF are augmented by chronic ACEI. 3. Increased plasma aldo levels do not rise during E in CHF before ACEI. 4. E raises lowered plasma aldo levels during chronic ACEI. The latter result suggests that chronic ACEI induces greater responsiveness by the adrenal cortex to the limited angiotensin II released during the physiologic stress of E in CHF.

HEMODYNAMIC EFFECT OF NITRATE THERAPY DURING ISOMETRIC EXERCISE IN PATIENTS WITH CHRONIC HEART FAILURE

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Isometric exercise (IEX) can lead to hemodynamic deterioration in patients (pts) with severe heart failure (CHF) due to increase in LV preload and afterload. Nitrate therapy has been proven beneficial both at rest and during dynamic exercise in pts with CHF. However, its hemodynamic effects during IEX has not been established. We evaluated the acute effect of 120mg transdermal nitroglycerin (TNTG) on hemodynamic changes mediated by IEX in 18 pts with severe CHF. Heart rate (HR), mean blood pressure (BP), right atrial (RA) and pulmonary artery wedge (PAW) pressures, cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and stroke work index (SWI) were measured at rest (C) and during IEX prior to (IEX1) and following TNTG (IEX2).

	HR	BP	RA	PAW	CI	SVI	SVR	PVR	SWI
C	98	94	10	27	2.2	23	1895	242	21
IEX1	104+	101++	14++	31++	2.0+	19++	2190+	277	19
IEX2	103	97	9**	22**	2.3**	22*	1892*	235	24*

+=P<0.05 ++=P<0.01 VS C *P<0.05 **=P<0.01 VS IEX1

SUMMARY: TNTG results in a significant hemodynamic improvement during IEX with a fall in right and left ventricular preload and afterload and a marked improvement in cardiac output and SWI.

CONCLUSIONS: Direct vasodilatory effect of TNTG counteracts IEX mediated hemodynamic deterioration in pts with CHF and leads to a significant improvement in right ventricular and LV function.

REGIONAL DISTRIBUTION OF CARDIAC OUTPUT AT REST AND DURING EXERCISE: EFFECT OF NIFEDIPINE

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The purpose of the study was to determine the effects of nifedipine on muscle blood flow during exercise in patients with coronary artery disease. Femoral vein flow (FVF) and cardiac output (CO) were measured by thermodilution in 6 patients before (Control) and after 20mg sublingual nifedipine (NIF). Haemodynamic measurements were made at rest and during bicycle exercise (50 watts). All patients were on chronic metoprolol therapy (100-200mg/day).

	REST		EXERCISE	
	Control	NIF	Control	NIF
VO_2 leg ¶	35±12	53±32	330±29	333±49
VO_2 total ¶	252±71	237±34	715±141	867±61
FVF(l/min)	0.4±0.1	0.8±0.6	2.8±0.4	2.6±0.4
CO(l/min)	4.5±0.9†	5.4±0.7	7.8±1.2*	10.6±2.1
%CO to legs	16±6	20±15	69±14§	52±5
SVR	20.2±3.2§	13.0±2.8	12.7±1.6§	7.7±1.6

mean±s.d. *p<0.05 §p<0.01 †p=0.02 ¶=mls/min

Leg and total body oxygen consumption were not different on NIF. Although NIF caused a significant reduction in systemic vascular resistance (SVR) and an increase in CO, there was no change in leg blood flow. Thus the proportion of cardiac output going to the legs during exercise decreased. We conclude that nifedipine increases rest and exercise cardiac output but does not increase oxygen delivery to peripheral exercising muscle due to a redistribution of cardiac output.

LARGE INCREASE IN PRELOAD ALTERS CARDIAC OUTPUT REGULATION DURING DYNAMIC EXERCISE

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The effect of large increases in preload on cardiac output regulation during exercise remains unclear. Head-out water immersion (WI), which produces a marked increase in central blood volume at rest and an associated rise in central venous pressure, was used to investigate the effects of an increase in preload on cardiac performance during exercise. Five healthy men aged 21-30 years were evaluated with a Swan-Ganz catheter while exercising upright on cycle ergometers on land (L) and with WI (32°C) at workloads corresponding to 40 and 80% maximal oxygen consumption (VO_2 max). Five hours rest separated the two tests and the order of testing was alternated. Mean (±SEM) RA pressure (RAP), CO, stroke volume (SV), and heart rate (HR) were: (*=p<0.05 WI vs L)

	Rest		40% VO_2Max.		80% VO_2Max.	
	L	WI	L	WI	L	WI
RAP,mmHg	1±1	13±2*	3±2	14±3	4±1	11±3*
HR,bpm	70±4	66±4	110±4	107±2	161±6	153±8*
SV,ml/min	74±17	122±22*	125±26	145±24*	129±30	150±34*
CO,l/min	5.1±1	7.9±1*	13.5±3	15.4±23*	20.5±5	24.4±5*

Core temperature on L and WI did not differ. The results indicate that at rest and at each stage of exercise, WI was associated with an increase in RAP (i.e., preload), SV and CO compared to L. These changes were all of greater magnitude than results from previous studies comparing upright and supine exercise suggesting that preload reserve is not maximally utilized during supine or upright exercise on land.

THE RELATION BETWEEN PEAK FILLING RATE AND EXERCISE TOLERANCE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION.

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Previous studies show no correlation between systolic left ventricular (LV) performance assessed as the ejection fraction (EF) and exercise (EX) tolerance. This study examined the relation between LV diastolic performance and EX tolerance in 63 patients (pts) with LV dysfunction (EF < 50%) due to known or suspected coronary artery disease. The 51 men and 12 women, aged 54 ± 8 years (mean ± SD) underwent upright EX testing on a bicycle ergometer starting at a workload of 200 kpm/min and increased by 100 kpm every 2 minutes. Radionuclide ventriculograms were obtained at rest (R) and peak EX. The EX end-points were angina (n:5), dyspnea (n:16) and fatigue (n:42). The pts were divided into: group 1 (n:28) had normal EX tolerance (9.5 ± 2.4 min), group 2 (n:18) had mild EX intolerance (5.8 ± 0.5 min) and group 3 (n:17) had severe EX intolerance (3.7 ± 0.9 min). The 3 groups did not differ in age, EX end-points, EF (R & EX), EX heart rate (HR), EX end-diastolic volume index (EDVI, ml/m^2), and LV peak filling rate (PFR, EDV/sec) at rest. The EX PFR was however significantly higher in group 1 (p = 0.03).

Group	REF	EX EF	EX HR	EX EDVI	R-PFR	EX PFR
1	40±8	43±13	131±26	115±37	1.8±0.7	3.7±1.8
2	33±9	38±10	120±28	122±35	2.0±1.0	2.9±2.2
3	38±8	38±11	118±22	125±34	1.6±0.5	2.2±1.1

Stepwise multivariate discriminate analysis of important variables, identified the EX PFR as the only predictor of EX tolerance (F = 6.0).
Thus, variation in EX PFR may explain the variability of EX tolerance in pts with LV dysfunction; pts with preserved EX capacity have higher EX PFR than those with EX intolerance.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #360/361
Mapping and Surgery for Cardiac Arrhythmias

MAPPING OF ENDOCARDIAL(ENDO) ACTIVATION DURING VENTRICULAR TACHYCARDIA(VT) - A "CLOSED-HEART" PROCEDURE

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Traditional ENDO mapping requires introduction of an exploring electrode through a ventriculotomy so that local timing data may be acquired sequentially from a conceptual grid. This is tedious and requires sustained runs of VT. Ventriculotomy, by disrupting the activation sequence and reducing wall tension, may make initiation of VT difficult or impossible. Furthermore, it may be associated with an increased morbidity and mortality if the incision is through friable ischemic or normal tissue, in contrast to scar. To overcome this, we developed an array of 110 silver bead electrodes stitched on a mesh over a latex balloon for ENDO recordings. At surgery, the array is passed via a left atriotomy into the intact LV and the balloon inflated with saline until stable electrograms are obtained. The balloon pressure is monitored to prevent LV ejection. All electrograms are recorded and displayed on-line by a previously described video-multiplex system. Induction of VT was rapid (< 4 min) and successful in 8/8 patients (pts), as opposed to 3/8 pts post-ventriculotomy. Of 16 episodes VT, ENDO mapping revealed incomplete circular activity in 12. Continuous circular activity (2) and figure of 8 patterns (2) were bridged by discrete low amplitude electrograms. Cautery applied to the electrode at earliest site of activation of VT, marked the site for subsequent surgical ablation. There were no complications related to the balloon. No VT could be induced in 5/5 pts at time of discharge. We conclude that ENDO mapping may be performed as a "closed-heart" procedure. Future electrical ablation via the ENDO electrode may obviate the need for ventriculotomy in pts without aneurysms.

SCINTIGRAPHY PROVIDES A THOROUGH EVALUATION OF "ELECTRICAL" AND MECHANICAL EVENTS DURING VENTRICULAR TACHYCARDIA

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In order to assess scintigraphic accuracy for the localization of the focus and evaluation of functional changes during ventricular tachycardia (VT), we studied 25 patients (PTS) during VT by radioangiography. Each had electrophysiologic study demonstrating 28 foci, 18 successfully mapped. The phase image (PI) during VT localized 6 RV, 10 septal and 12 LV foci which corresponded to the same or adjacent EPS sites in 14 and matched ECG findings in 10 others, including 2 PTS with multiple foci. Accurate PI were acquired with as little as 40 sec of data, despite poor LV function, and often influenced EPS. When compared to rest radioangiography in 19 PTS, hemodynamic deterioration during VT in 8 PTS related to a higher mean VT rate (159) and a greater relative fall in end-diastolic volume (.74), stroke volume (.31) and cardiac output (.62) compared to these values in 11 PTS tolerant to VT during scintigraphic study (127, .94, .64, 1.25, respectively, all $p<0.05$). Hemodynamic deterioration was also related to greater dysynchrony in wall motion and a lower ejection fraction during VT (.28 vs. .13, $p<0.05$).

Radioangiography with PI analysis can accurately localize the focus, characterize functional changes and complement EPS in VT evaluation. It provides insight into the cause of hemodynamic intolerance during VT.

ECHOCARDIOGRAPHIC LOCALIZATION OF THE SITE OF ACTIVATION IN VENTRICULAR TACHYCARDIA AND VENTRICULAR PRE-EXCITATION.

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Noninvasive localization of the site of ventricular activation (SVA) in patients (pts) with ventricular tachycardia (VT) or Wolff-Parkinson-White syndrome (WPW) may be a useful adjunct to invasive mapping. Two-dimensional echocardiograms (2DE) were performed during hemodynamically stable VT (5 pts; 1 pt with 2 VT morphologies) or during sinus rhythm in pts with WPW (7 pts). The SVA of VT was identified at electrophysiologic study (EPS) in all pts. The SVA in pts with WPW was localized by delta wave polarity on 12-lead electrocardiogram (ECG) in 7 pts and confirmed by EPS in 5 pts. Short axis and apical 4 chamber views of the left ventricle were analyzed by computer assisted segmental wall motion analysis and the SVA was determined by an observer blinded to the results of ECG and EPS localization. In 6 episodes of VT, 2DE identified the SVA as upper septum in 2, inferior septum in 2, posterior wall in 1 and lateral wall in 1 and correlated with EPS mapping in 5/6 cases. A posterior basal site was incorrectly identified by 2DE as lateral wall. In WPW pts, the SVA determined by 2DE was anterior in 3, left anterior paraseptal in 2, left posterior paraseptal in 1 and right anterior in 1 and correlated with EPS and ECG localization of SVA in 5/7 pts. A right paraseptal tract was incorrectly identified by 2DE as left paraseptal and a left posterior tract as anterolateral in a pt with an inferior posterior infarct. Thus, computer assisted segmental wall motion analysis of 2DE accurately identified the SVA in the majority of cases and this noninvasive method may be a useful adjunct in localizing the origin of dysrhythmias.

IDENTIFICATION OF INITIAL SITE AND SEQUENCE OF VENTRICULAR CONTRACTION BY FOURIER PHASE ANALYSIS OF TWO DIMENSIONAL ECHOCARDIOGRAMS.

James A. Rothendler, M.D., F.A.C.C., Edgar C. Schick, M.D., F.A.C.C., Mary Jane Birmingham, B.A., Thomas J. Ryan, M.D., F.A.C.C. Boston University Medical Center, Boston, Massachusetts.

A noninvasive means to identify the initial site and quantitate the sequence of contraction of the left ventricle (LV) from a single cardiac cycle could be used to investigate both disorders causing dyssynchrony of contraction and the locus of ectopic LV activation. We applied Fourier phase analysis (FPA) to digitized two dimensional echocardiograms (2DE) in 16 patients, 8 with right ventricular endocardial pacemakers and 8 normals, to determine the applicability of FPA. The mean heart rate was similar between the two groups (73±12 vs. 71±7, normal vs. paced, P=NS). Phase maps were generated by determining the phase angle for each pixel within a region in proximity to the endocardial surface of the LV during a single cardiac cycle. Maps from paced patients, all correctly distinguished from the normals by blinded reading, displayed: 1) earliest phase angles in the apical-septal region of the LV with progression to the basal and posterior walls consistent with the site of artificial pacing; 2) a larger dispersion in phase angles compared to normals (124°±45° vs 54°±11°, $P<.01$) consistent with more dysynchrony of mechanical contraction as a result of the abnormal electrical activation pathway.
We conclude: 1) FPA of 2DE accurately identifies and quantifies the onset and sequence of LV contraction, and 2) this technique provides a useful non-invasive tool for study of abnormal LV activation from single cardiac cycles.

LONG-TERM SURVIVAL AFTER LEFT CERVICO-THORACIC SYMPATHECTOMY IN HIGH RISK LONG QT SYNDROME PATIENTS WITH REFRACTORY VENTRICULAR ARRHYTHMIAS.

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In 1969, on the basis of clinical and experimental observations, left cervico-thoracic sympathectomy (LCTSX) was introduced for the therapy of patients (pts) with long QT syndrome (LQTS) refractory to conventional therapy. During the past 16 years, 56 LQTS pts worldwide have had LCTSX. Detailed information is available on 51 pts: 82% are females, 6% had congenital deafness, 45% had family history of LQTS; mean age at LCTSX was 22 yrs (range 1 to 58 yrs). Before LCTSX surgery, all pts were symptomatic and 60% had prior cardiac arrest; 77% failed to respond to beta blockers (BB). The exact extent of surgery was not known in all pts: 39 pts (76%) had adequate denervation (ablation of the lower-midportion of 7th cervical ganglion to 3rd-4th thoracic ganglia), 5 pts required a second, more extensive sympathectomy due to inadequate initial LCTSX surgery. Follow-up was available in 49/51 pts: the mean follow-up was 4.8 yr/pt (range 0.5 to 16 yrs). Following LCTSX, 80% of the pts continued BB therapy alone or combined with other drugs and 12 pts (20%) had pacemaker implantation for better control of symptoms. Using life-table analysis, survival at 1, 3 and 7 yrs after LCTSX was 94%, 91% and 86%, respectively. In conclusion, in high risk LQTS pts with malignant ventricular arrhythmias refractory to conventional medical treatment, LCTSX is associated with very favorable long-term survival.

FEASIBILITY OF CRYOABLATION OF THE POSTERIOR PAPILLARY MUSCLE IN THE DOG. Gerard M. Guiraudon, M.D., F.A.C.C., Douglas L. Jones, PhD., George J. Klein, M.D., F.A.C.C., William J. Kostuk, M.D., F.A.C.C., George Jablonsky, M.D., F.A.C.C., Douglas G. McLellan, M.A., James L. M. MacDonald, C.C.P., University Hospital, London, Ontario.

The posterior papillary muscle (PPM) may be part of the arrhythmogenic zone in patients undergoing surgery for ventricular tachycardia and this may necessitate its resection for cure of the arrhythmia. Cryoablation of the PPM or its ventricular attachment is feasible but the hemodynamic consequences and the effects on mitral valve (MV) function are unknown. We studied the hemodynamic effects of extensive cryoablation of the PPM in dogs (weighing 25-30kg) who had their PPM and the ventricular attachment cryoablated under cold cardioplegic cardiac arrest. A circular cryoprobe (diameter 1.5cm, -60°C for 2 minutes was applied both to the endocardium and epicardium to achieve this. Hemodynamic measurements and LV angiography were obtained prior to cryosurgery and 4 weeks postoperatively after which the hearts were excised for pathological examination. Cryosurgery of the PPM resulted in no change in arterial pressure (116-81 vs 118-84mm Hg), left ventricular dP/dT (1840 vs 1740), mean pulmonary capillary wedge pressure (8 vs 7.5mm Hg) and cardiac output (2.71 vs 2.16L per min). Left ventricular angiograms were unchanged with no evidence of mitral insufficiency preoperatively or postoperatively. Pathological examination showed homogeneous dense fibrosis of the PPM and its ventricular attachment well delineated from normal muscle. There was no bulging or thinning of the LV wall and no necrosis outside the cryoablated area.

We conclude that cryoablation of the PPM and its attachment does not impair MV function in the dog. It may be an alternative to resection and MV replacement in patients with arrhythmias originating in this area.

Thursday, March 13, 1986
10:30AM-12:00NOON, Room #360/361
Arrhythmias—Electrical and Laser Ablation Techniques

EFFECTIVENESS OF ELECTRICAL CATHETER ABLATION FOR VENTRICULAR TACHYCARDIA: FOLLOW-UP WITHOUT ANTI-ARRHYTHMIC DRUGS. Richard N. Hauer, M.D., Etienne O. Robles de Medina, M.D., F.A.C.C., Paul J. Kuijer, M.D., Pieter W. Westerhof, M.D., University Hospital, Utrecht, The Netherlands.

Electrical catheter ablation(ECA) for chronic recurrent ventricular tachycardia(VT) was performed in 5 pts (2 chronic ischemic, 1 congenital and 2 with primary electrical heart disease), using rigid criteria to define the arrhythmogenic site(AS). These criteria were:1) During VT reproducible recording of the earliest obtained local diastolic activation(DA).2) A fixed relationship of DA to the subsequent QRS complex of VT during spontaneous or pacing induced change of the RR interval. All pts proved refractory or intolerant to at least 3 anti-arrhythmic drug trials. The number of VT episodes during 3 months preceding ECA was: 2 in 2 pts, 6 in 1 pt and more than 20 in 2 pts. Endocardial catheter mapping was performed using simultaneous bipolar and unipolar recordings. The AS was localized in the left ventricle in 3 pts and in the right ventricle in 2 pts. The interval between DA and the onset of QRS at the AS was 5, 10, 60, 90 and 130 ms. A single R wave synchronized 250 J cathodal shock was delivered at the AS using an external chest paddle as the anode. One pt had symptomatic sustained VT episodes during the first 3 days after the shock, otherwise no complications occurred. All pts were discharged off anti-arrhythmic drugs and followed for a mean 3.5 ± 2.5 months. There was no recurrence of VT in 4 pts. In 1 pt VT episodes with identical morphology recurred. Our results indicate:1. ECA without additional drug treatment is promising in pts with VT. 2. Efficacy with less energy than previously reported may be due to rigid criteria for AS localization. 3. ECA itself can provoke VT in the first days after the shock.

VENTRICULAR ARRHYTHMIAS DURING ENDOCARDIAL CATHETER FULGURATION OF VENTRICULAR TACHYCARDIAS. J.L.Tonet, MD, M.Baraka, MD, G.Fontaine, MD, FACC, S.Abdelali, MD, R.Frank, MD, L.Menezes Falcao, MD, C.Funck-Brentano, MD, Y.Grosgogeat, MD, FACC. Hôpital Jean Rostand, Paris-Ivry, France.

31 consecutive patients (pts) (mean age 48 yrs, 26 men) with chronic refractory ventricular tachycardias (VT) underwent endocardial catheter fulguration (F). 13 had prior myocardial infarction, 11 arrhythmogenic ventricular dysplasia, 4 idiopathic dilated cardiomyopathy, 1 operated congenital anomaly, and 2 had normal hearts. Cardiomegaly was present in 20 pts. None were receiving digitalis or class I antiarrhythmic drugs at the time of F, 17 pts (55%) were on amiodarone. 167 shocks (82 in the LV) of 160 to 320J (mean 210J, 3J/kg) were delivered between the distal pole (anode) of a selected catheter and a posterior external chest plate, 129 during VT, 38 in sinus rythm (SR). Mean peak of creatine kinase reached 306 ± 354, MB fraction 40 ± 30 UI/l.

25 shocks (15%) caused 13 ventricular fibrillation (FV) and 12 VT (14 shocks in the LV, 13 properly synchronized); 23 were done during VT and 2 in SR ($.05<p<.10$). There is no relation between : sites of shock in the ventricles, type of heart disease, amount of energy delivered, peak of creatine kinase, weight of pts, and these arrhythmias. Surprisingly, timing of shock with respect to QRS surface did not affect the frequency of VF or VT.

We conclude: 1) Endocardial shocks of 210J had a propensity to initiate ventricular arrhythmias. 2) Properly synchronized endocardial shocks delivered during VT or SR may produce VF or VT. 3) Endocardial shocks of 210J has minor defibrillatory properties. 4) Because VF and VT during F are usually not transient, anterior patch electrode for immediate cardioversion is mandatory.

PATHOLOGICAL AND CLINICAL OBSERVATIONS AFTER CATHETER FULGURATION IN MAN Richard W. Henthorn, M.D., F.A.C.C., Mark D. Cohen, M.D., Peter G. Anderson, D.V.M., Andrew E. Epstein, M.D., F.A.C.C.,Vance J. Plumb, M.D., F.A.C.C., Brian Olshansky, M.D., Albert L. Waldo, M.D., F.A.C.C. University of Alabama at Birmingham, Birmingham, Alabama

We performed catheter fulguration (FLG) guided by catheter mapping in 8 patients (pts) with sustained monomorphic ventricular tachycardia. In 5/8 pts, cardiac tissue was available for study: 3 from surgical resections (6, 6, and 13 days post-FLG) and 2 from autopsy material (6 and 190 days post-FLG). These 5 pts with coronary artery disease (CAD) status post myocardial infarction and a mean ejection fraction (EF) of .17±.06 underwent FLG with delivery of 200 or 300 joules (J) (533±821 J/pt) between the distal electrode of a 6 French catheter and a back paddle, or 100J across the septum using the distal electrodes of 2 catheters. The 5 pts developed CPK rise of 204±65 IU/L and CPKMB of 31±17 IU/L. Only 1/5 pts had an identifiable pathologic lesion, which was 4 mm in depth and 14 mm at its widest point composed of coagulated myocytes and thrombotic material adherent to the endocardial surface. FLG lesions were not discernible in the other 4 pts whose FLG sites were composed of mineralized scar or adherent thrombotic material. Three of the 8 pts undergoing FLG (333±58J) had pre and post-FLG 2-D echocardiography (2-D). One of the 3 pts had primary electrical disease (EF=.56) and a post-FLG (400J) CPK rise of 809 IU/L, MB of 210 IU/L. The post-FLG 2-D showed a new dyskinetic area at the FLG site. The other 2 pts had CAD with a mean EF of .18 and a post-FLG (300J) mean CPK rise of 226 IU/L, mean MB rise of 44 IU/L. These 2 pts had no discernible 2-D change. Conclusions: 1) Demonstrable pathological and/or 2-D changes were evident only in pts who underwent FLG at sites of apparently normal myocardium; 2) There was significant variability of FLG tissue destruction dependent on whether normal or scarred myocardium was fulgurated.

INTERCATHETER ENERGY DELIVERY FOR ABLATION OF VENTRICULAR MYOCARDIUM Alan H. Kadish, MD, Joseph F. Spear, PhD, FACC, Charles Prood, MA, Joseph H. Levine, M.D. and E. Neil Moore, DVM, PhD, FACC University of Pennsylvania, Philadelphia, Pa.

We delivered 12 50 joule shocks through endocardial catheters in 12 anesthetized dogs. In 6, a back paddle was used as the anode (AN). In six intercatheter ablations (ICA) a second nearby epicardial or coronary sinus catheter served as the AN. We measured current and voltage with a custom made electronic device and calculated impedance, power, and total energy. Mean Results:

Anode	V	I	R	E	Sz
Back Paddle	1499	9	176	46	14
Catheter	1165	34*	15*	59	17**

* p<0.05; **=.07; V=peak voltage (volts); I=peak current (amps); R=Impedance at peak I; E= total energy (joules); Sz=lesion size. During ICA, peak currents were high and delivered energy was higher than set energy, presumably because standard defibrillators do not provide accurate energy delivery at low impedance. When an epicardial catheter was used as the AN, epicardial and endocardial necrosis were similar. In 3 shocks the epicardial catheter was placed at a point distant from the endocardial catheter. Distinct lesions were produced at both AN and cathodal site. Damage was asymmetric extending 2 times further in the area between electrodes than away from the opposite pole. We conclude: 1) Varying AN position can determine the direction of tissue injury during ICA.2) Equal damage occurs around both the AN and cathode presumably because of similar high current density. 3) Although the ability to direct tissue injury is a potential advantage of ICA, damage to both AN and cathodal areas, high peak currents, greater tissue damage and a trend towards higher than set energy delivery must be taken into account in any potential clinical use.

LASER ABLATION LEADS TO MORE FOCAL ELECTROPHYSIOLOGIC EFFECTS COMPARED TO CATHETER DELIVERED, HIGH ENERGY ABLATION. John E. Merillat, M.D., Joseph H. Levine, M.D., Harlan F. Weisman, M.D., Michael D. Stern, M.D., Joseph F. Spear, Ph.D., F.A.C.C., E. Neil Moore, D.V.M., Ph.D., F.A.C.C., Alan A. Kadish, M.D., James Fonger, M.D., Raul Guzman, B.S., Thomas Guarnieri, M.D., F.A.C.C., The Johns Hopkins University, Baltimore, MD

Laser ablation (L) in animals is associated with fewer arrhythmias and less regional wall motion abnormality when compared to catheter delivered high energy (HE), possibly due to the more focal injury produced by L. We examined this question by comparing the electrophysiologic effects associated with a small matched 1-1.5 mm region of visible necrosis produced with either argon L (3.5 Watts over 4 seconds via 200 micron quartz fiber) or HEA (10-20 Joules via a cathode 1 mm in diameter) in 11 normal canine epicardial preparations. Comparisons were made of action potential amplitude (APA), DV/DT, and resting potential (RMP) at varying distances from the center of the necrotic zone. RESULTS (m±sd):

	RMP (mv)			DV/DT (Volts/sec)			APA (mv)		
Distance (mm)	2	5	10	2	5	10	2	5	10
HE (n=5)	21±11	52±9	69±9	1±2	8±10	96±45	5±10	23±19	74±9
L (n=6)	70±17	81±5	78±6	58±31	87±18	91±11	64±37	93±8	92±14
	p <.001	.0001	ns	.01	.00001	ns	.01	.0001	ns

CONCLUSION: Action potential abnormalities and the border zone of depressed tissue were more extensive following HEA vs. LA at energy levels that yield comparable area of central necrosis. The more focal electrophysiologic effects of LA may explain its less frequent association with arrhythmias and regional wall motion abnormality.

SUCCESSFUL INTRAOPERATIVE Nd:YAG LASER ABLATION OF VENTRICULAR TACHYCARDIA. Robert H. Svenson, MD, FACC, John J. Gallagher, MD, FACC, Jay G. Selle, MD, Will C. Sealy, MD, Samuel H. Zimmern, MD, FACC, John M. Fedor, MD, FACC, Marie-Claire Marroum, MD, G.P. Tatsis, BS, K.T. Seifert, MS, Francis Robicsek, MD, FACC. Sanger Clinic P.A., Heineman Research Center, and Carolina's Heart Institute, Charlotte, N.C.

We recently utilized intraoperative Nd:YAG laser photocoagulation to treat 5 patients (pts) with drug resistant ventricular tachycardia (VT). All pts underwent preoperative electrophysiologic studies (EPS), intraoperative mapping, intraoperative EPS postlasing and EPS on the 7-9th postoperative day. All pts had coronary disease but only pts 1-4 had a previous myocardial infarction. Following informed consent intraoperative mapping was performed to locate the origin of the VT. Pts 1-4 had sites of VT origin >6 cm apart. Lasing was performed in sinus rhythm or VT. A continuous wave Nd:YAG laser coupled to a 600 μ gas cooled fiber delivered radiation at 30 and/or 50 watts with a spot size of$\simeq$0.5 cm. Operative data is summarized below.

Pt	No. VT Morph	VT Site	Lased area (cm^2)	Joules per cm^2	EF pre	EF post
1	2	AS,IS	18	1003	.29	.31
2	2	A, S	24	772	.18	.20
3	2	L, S	31	967	.26	.29
4	4	BS,S,A	42	1629	.24	.28
5	1	IS	24	966	.18	.27

(A=anterior freewall, AS=anterior septal margin, BS=basilar septum, L=lateral freewall, IS=inferior septal margin, S=septum, EF=ejection fraction). Following lasing delayed potentials were abolished and VT could not be induced intraoperatively or 7-9 days postop. Pts 1-3 had no inducible VT 6-8 wks postop. Pts 4 and 5 have been followed less than 6 wks. Nd:YAG laser photocoagulation is a promising new technique for the surgical therapy of refractory VT. It can be performed safely without adverse effects on ventricular or valvular function.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #366/367
Considerations in Angioplasty and Laser Ablation

MULTIPLE VESSEL ANGIOPLASTY: DEFINITION, CLASSIFICATION AND RESULTS. Richard K. Myler, M.D., FACC, Giles Cote, M.D., Eric J. Topol, M.D., Simon H. Stertzer, M.D., FACC, Jodi Fishman-Rosen, R.N., M.S., Mary C. Murphy, R.N., M.S. San Francisco Heart Institute, Daly City, CA

Coronary angioplasty (PTCA) was performed in two or more major vessels in 313 consecutive patients (P) with 690 vessels (V) treated. In this cohort, the age range was 32-78 yrs. (m = 57), 81% were males; 82% had two vessel, 16% three vessel, and 2% four vessel angioplasty. Success was achieved in 95% of P and 89% of V. Ten patients (3.2%) required emergency coronary bypass surgery (CABG), with 6 sustaining myocardial infarction. There was 1 death (0.3%). Patients were divided into 2 groups: Group A - single lesions in two or more vessels (162 P, 351 V); Group B - complex lesions in at least one of the vessels treated (151 P, 339 V). Chi-square analyses of success and complications indicated a trend towards a higher incidence of MI and recurrence (p = .16) in Group B vs. Group A. However, no statistically significant difference was noted in the success rate or incidence of emergency CABG. Ninety-six percent of Group A patients had the entire angioplasty performed at one time, whereas in Group B - 88% (p = .09) did; the other 12% had the angioplasty staged over 2 days. Repeat PTCA of patients with recurrence showed 94% success, but a 6% emergency CABG. Thus, multiple vessel angioplasty in carefully selected patients can be performed as safely and effectively as with single vessel disease. The vast majority can have all vessels treated at one time, though staging the procedure might be advisable in selected complex (Group B) patients. Repeat PTCA in multivessel patients with recurrence, although as effective, may not be as safe as redo PTCA in single vessel angioplasty patients.

CORONARY ANGIOPLASTY (PTCA) FOR TOTAL CORONARY OCCLUSION: SUCCESS RATE AND FOLLOW-UP

Raoul Bonan, M.D., F.A.C.C., Simon Kouz, M.D., Jacques Crépeau, M.D., Jacques Lespérance, M.D., and Pierre Théroux, M.D., F.A.C.C., Montreal Heart Institute, Montreal, Canada.

From June 1984 to June 1985, PTCA was attempted in our Institution in 478 coronary artery segments in 393 pts. In 32 of these pts, a previously documented stenosis (S) had progressed to complete coronary occlusion without myocardial infarction (MI). The primary success rate in these 32 pts was 65% compared to 87% for all PTCAs ($p<.05$) and similar whether the left anterior descending (6/9), the circumflex (7/9) or the right coronary artery (8/13) was dilated. The residual (S) averaged 32.1%±13.1% and the trans-occlusion gradient was reduced from 49±12 to 13±9 mmHg ($p<.001$). The time elapsed between initial documentation of (S) and PTCA was shorter when it was successful (3.4±4 vs 7.3±7mo., $p<.05$). The success rate was 80% when this time interval was less than 3 mo. and 50% when it was more ($p<.05$). The severity of the initial (S) did not influence results. Complications associated with the procedure were a non-sustained ventricular tachycardia in 1 pt, and a prolonged chest pain without MI in one. After a mean follow-up of 6±2 mo., 13 of the 21 dilated pts were symptom-free, 6 had improved angina and 2 did not. A treadmill exercise test induced ischemia in only 3 pts. Control angiography in 11 pts showed restenosis ≥70% in 3, two had successful redilatation; in the 8 others the (S) was 36.2±22% vs 24.4±16% just after PTCA (NS).

Thus PTCA in total coronary obstruction has a high success rate particularly when attempted early after the obstruction; the procedure appears safe and associated with good long-term results.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY OF PROTECTED AND UNPROTECTED LEFT MAIN CORONARY STENOSIS

Gary Gershony, M.D., F.R.C.P.(C), Pierre Abi-Mansour, M.D., James Wilentz, M.D., Gary Roubin, M.B., Ph.D., Nancy Braman, R.N., Beverly Mellen, B.A., Andreas Gruentzig, M.D., F.A.C.C. Emory University School of Medicine, Atlanta, GA

Initial experience with percutaneous transluminal coronary angioplasty (PTCA) of left main (LM) stenoses suggested an increased risk of early and late complications due to the extent of jeopardized myocardium. We analyzed the results in 17 patients (pts) undergoing 20 dilatation procedures of LM stenosis between July 1981 and August 1985. Ten dilatations were performed in 9 pts without prior coronary artery bypass graft surgery (CABG), "unprotected", either as palliative procedures when CABG was contraindicated or early in the PTCA experience. Ten dilatations were performed in 8 pts with prior CABG either for progression of native disease or partial graft failure. In this group, part of the LM distribution thus remained "protected". There were 13 males, 4 females, with a mean age of 54 years. Mean duration of anginal symptoms was 21+30 (mean+SD) months. The primary success rate was 18/20 (90%). Mean percent diameter stenosis pre- and post-PTCA was 70+14 and 32+16 respectively. The mean post-PTCA transstenotic gradient was 12+7mmHg. There were no in-hospital deaths. Of the 10 "unprotected" procedures, 2 pts required emergency CABG and 1 of these had a myocardial infarction. No acute major complications occurred in the "protected" group. Of the 18 successfully dilated stenoses, 9 underwent restudy angiography 7+3 months after PTCA. Five of these 9 (56%) demonstrated restenosis. Conclusions: 1) PTCA of LM stenosis can be performed safely in the setting of "protected" myocardium. 2) Because of the risk of complications and restenosis "unprotected" LM should remain a relative contraindication to PTCA.

PULSE DURATION IS THE MAJOR DETERMINANT OF THERMAL DAMAGE DURING PULSED LASER TISSUE ABLATION.

Lawrence I. Deckelbaum, M.D., Joseph K. Lam, A.S., Soni Clubb, B.S., and Henry S. Cabin, M.D., F.A.C.C. West Haven VAMC and Yale University, New Haven, CT.

Successful cardiovascular applications of lasers may require focal ablation of tissue without thermal damage to adjacent tissue. This has been achieved during pulsed laser ablation using low repetition rate, high pulse energy, and short pulse duration. Because the resultant high peak power (pulse energy/pulse duration) impedes fiberoptic coupling, we evaluated whether prolonging the pulse duration to decrease peak power would alter laser tissue ablation. The peak power of a Nd:YAG laser (wavelength 1064 nm, repetition rate 10 Hz) was altered by prolonging the Q-switched (Q) pulse duration of .01 μs to 200 μs using non-Q switched (N) pulsing. Sixty 3-mm thick myocardial slices were irradiated in air using pulse energies of 200 mJ in N and Q modes. All parameters of laser irradiation were identical except for pulse duration. As a result, peak energy was 1.0 kilowatt in N mode and 20 megawatts in Q mode. The energy required to bore a hole in the myocardial slices was markedly increased in the N versus Q mode (813 ± 62 (M ± SEM) versus 16 ± 2 Joules). Tissue temperature measured by a thermocouple 1 mm from the hole rose to 62 ± 3°C in N mode compared to only 25 ± 1°C in Q mode. Gross, light and scanning electron microscopic examination all revealed evidence of thermal boundary damage with N but not with Q mode.

Conclusion: Short pulse duration is crucial to eliminate thermal damage during pulsed laser tissue ablation. Increasing pulse duration to decrease peak power decreases the efficiency of tissue vaporization and increases heat diffusion and thermal injury to adjacent tissue.

ABSOLUTE CROSS SECTIONAL AREA QUANTITATION OF CORONARY STENOSIS USING A NEW ONE VIEW VIDEODENSITOMETRIC METHOD.

Joseph Wiesel, M.D., Andrew M. Grunwald, M.D., F.A.C.C., Bruce Robin, Monty M. Bodenheimer, M.D., F.A.C.C. Long Island Jewish Medical Center, New Hyde Park, New York.

Absolute cross sectional area (CSA) of a stenosis best reflects hemodynamic severity. Edge detection (ED) algorithms alone require two orthogonal views for angiographic quantitation of irregular lesions. While videodensitometry (VDS) requires only one view, it provides only relative but not absolute data on CSA. Therefore, we evaluated a combined approach using ED to determine the CSA of a normal segment and VDS to determine the percent narrowing of an adjacent stenosis. The absolute CSA of the stenosis is calculated from these two results. We validated this new combined method (ED-VDS) by comparing it to the standard two view ED method in 8 anesthetized closed chest dogs. Ten plastic cylinders with precisely measured circular and irregular lumens were inserted into the coronary arteries and digital angiograms recorded. A first derivative ED method with an operator interactive VDS program was used. With the diameter of the angiographic catheter as the measurement standard, ED was used to compute the circular CSA of a normal arterial segment. The CSA of the stenoses were computed based on the VDS ratio of the normal and stenotic segments for each view independently. The two view ED method used two orthogonal views to calculate the CSA. The mean and standard deviation of the absolute differences between the true CSA of the cylinders and the ED/VDS method was .45±.53 and the two view ED method was .91±.42 sq mm. The correlation for the ED/VDS method (r=.87) was slightly higher than the two view method (r=.75). The new one view ED/VDS method is as accurate as the two view ED method to quantitate CSA of stenoses.

SAFETY OF BETA BLOCKERS WITH CORONARY ANGIOPLASTY.
Mitchell W. Krucoff MD, Lowell F. Satler MD FACC, Kenneth M. Kent MD PhD FACC, Carolyn J. Ewels BS, Susan W. Ahmed PhD, Ross D. Fletcher MD FACC, Charles E. Rackley MD FACC, Georgetown University, Washington, D.C.

Calcium blockers with vasodilator properties are presumed to be superior to beta blockers after angioplasty. To compare the incidence of ischemic episodes after angioplasty with beta blockers to the incidence with calcium blockers, 3 channel continuous ST segment recording was performed in 40 consecutive patients undergoing single vessel angioplasty. Recordings were performed over 198 hours following angioplasty in 12 patients treated with beta blockers and compared to data base recordings of 503 hours in 28 patients treated with calcium blockers. ST changes on Holter were documented by recording during balloon occlusion of the coronary during angioplasty. Maximum ST elevation relative to baseline during angioplasty was 2.5 $\pm$ 1.3mm in the beta blocker group and 2.6 $\pm$ 1.9mm in the calcium blocker group (NS). Recording then continued for a mean of 18 hours after angioplasty. Mean heart rate was 58 $\pm$ 7 in the beta blocker group versus 74 $\pm$ 7 in the calcium blocker group ($p < .05$). There was 1 post-angioplasty infarct in each group (NS). With calcium blockers, there were 12 episodes recorded in 6 patients totaling 8.6 hours. There were no episodes of ischemia in the beta-blocked group (NS). Thus: 1) angioplasty induces equivalent ischemia in patients on beta blockers or calcium channel blockers; and 2) beta blockade is not associated with an increased incidence of episodes of ischemia after angioplasty.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #366/367
Electrocardiographic Evaluation of Ischemia and the Effects of Interventional Therapy

VALIDATION OF A DEVICE FOR AMBULATORY MONITORING AND ON-LINE ANALYSIS OF ISCHEMIA IN PATIENTS WITH ANGINA.
Joan Barry, B.A., Elizabeth E. Nabel, M.D., Michael B. Rocco, M.D., Stephen Campbell, M.D. and Andrew P. Selwyn, M.D., FACC. Brigham & Women's Hospital, Boston, MA.

Patients with angina and coronary artery disease have frequent episodes of asymptomatic myocardial ischemia demonstrated with frequency modulated (FM) holter recordings. In order to assess the clinical use of on-line analysis of ischemic ST depression (STD), long term monitoring, and an audible beep that can interact with patients, we evaluated a programmable microprocessor EKG monitor (Q-Med) for detection and measurement of ischemic STD episodes. For validation, 22 patients with chest pain underwent diagnostic exercise tests. Q-Med detected 9 of 9 episodes of significant STD with comparable measurement of degree and duration with the standard Marquette EKG and 12 of 13 negative results (1 false positive). In 4 of the 5 patients developing symptoms, an audible beep preceded the onset of chest pain correctly (no false positives). Additionally, 5 ambulant patients with angina and coronary disease underwent simultaneous FM holter and Q-Med recordings for STD. Q-Med detected 5 of 5 episodes of ischemic STD correctly with no false positives registered in 111 hours of simultaneous recordings. This preliminary analysis suggests that Q-Med appears to be accurate in the detection and quantification of STD. The device is capable of long term monitoring and a beep preceding ischemic chest pain may permit patient interaction prior to the development of symptoms.

REGIONAL MYOCARDIAL BLOOD FLOW CORRELATES OF ISCHEMIC S-T SEGMENT DEPRESSION.
David M. Mirvis, M.D., K. B. Ramanathan, M.D., Jack L. Wilson, PhD, University of Tennessee, Memphis, TN

Tachycardia produces subendocardial ischemia and S-T segment abnormalities after coronary obstruction. To determine if a quantitative relation exists between the onset of S-T shifts and transmural blood flow, 19 dogs were studied. Coronary obstruction was produced by ameroid constriction of the left circumflex artery in 14 dogs, and tachycardia was generated by incremental atrial pacing at 90 to 210 beats/min. S-T shifts were studied by body surface isopotential maps using an 84-electrode torso grid, and blood flow was quantitated by serial radiolabelled microsphere injections. Isopotential maps at each paced rate, 40 msec into S-T segment, were classified as normal or ischemic based upon spatial patterns of voltages. Pacing after 3 weeks of ameroid constriction reduced endo/epi flow ratios in 11 dogs from 1.16 $\pm$ 0.22 at rest to 0.41 $\pm$ 0.18 at 210 beats/min. Abnormal S-T depression with ischemic map patterns developed at 184.0 $\pm$ 16.5 beats/min. Endo/epi ratios at rates with ischemic S-T pattern (0.45 $\pm$ 0.15) were lower than at those with normal S-T maps (1.05 $\pm$ 0.19, $p<0.01$). Heart rate, perfusion bed size (determined by dye infusion), and endo/epi ratios were entered into a logistic regression model to determine which were predictors of an ischemic S-T pattern. Only the endo/epi flow ratio was a significant predictor of S-T patterns; a 95% probability of an ischemic pattern corresponded to a endo/epi ratio of $\leq$ 0.58, while a 95% probability of a normal S-T pattern occurred with a flow ratio of $\geq$ 0.76 ($p<0.01$). Using this model, 95.5% of cases were correctly classified. Neither heart rate nor perfusion bed size were predictors. Thus, onset of S-T changes of ischemia corresponds to a predictable degree of flow redistribution.

TRANSIENT ISCHEMIA IN CORONARY DISEASE IS ASSOCIATED WITH MENTAL AROUSAL DURING DAILY LIFE
George S. Rebecca, M.D., Richard R. Wayne,B.S., Stephen Campbell, M.B., Michael Rocco, M.D., Elizabeth Nabel, M.D., Joan Barry, Andrew P. Selwyn, M.D., FACC. Brigham & Women's Hospital, Harvard Medical School, Boston, MA.

Patients with angina and coronary disease have frequent asymptomatic episodes of ischemic ST depression (STD) during daily life. We tested the hypothesis that the majority of events are associated with routine activities demanding mental arousal. Twenty-one patients with chronic stable angina (CSA), positive exercise tests and proven coronary disease underwent 891 hours of frequency modulated holter monitoring to measure episodes of STD ($\geq$ 1 mm, $\geq$80 msec, and lasting $\geq$30 seconds duration) and demonstrated 233 episodes of transient ischemia with 87% being asymptomatic. A structured diary of mental (usual events, stress) and physical state (rest, usual, exercise) were used to specify activities and on review showed that 19% of episodes occurred while asleep, 18% occurred at physical rest, 52% during minimal physical activity, with 11% during exercise. In contrast 6% of episodes occurred during mental stress but 75% occurred in association with tasks demanding routine mental work (conversation, office work, reading, watching TV). STD was most often related to mental arousal even when the number of episodes was normalized for time spent at each activity. (Chi Square χ^2 $p < .001$). Thus, episodes of transient ischemia were most commonly associated with activities demanding mental arousal and not physical exertion. This new characteristic describes the most frequent trigger associated with myocardial ischemia during daily life and may have therapeutic implications as behavior and levels of stress can be modified.

PAINLESS MYOCARDIAL ISCHEMIA IN CHRONIC STABLE ANGINA. ITS RELATION TO EXERCISE TOLERANCE AND CORONARY ARTERIOGRAPHY

Francesco Romeo MD, Sergio Chierchia MD, Attilio Maseri MD, FACC. Cardiovascular Unit, RPMS, Hammersmith Hospital, London, UK.

Although the occurrence of painless myocardial ischemia is well recognized, its incidence in an unselected population of patients (pts) with chronic stable angina (CSA), and its relation to exercise tolerance and severity of coronary artery disease (CAD) are not known.

We studied 84 consecutive pts with CSA, positive exercise test (ET) and documented CAD. All underwent ambulatory ECG monitoring for 48 hours, off medication apart from nitroglycerin. Recordings were performed using FM Holter boxes, within 2 weeks of coronary arteriography and ET. In the period of monitoring, 49 pts (58%, Group 1) had episodes of diagnostic ST segment depression and 35 (42%, Group 2) did not. Of the Group 1 pts 6, 18 and 75% had 1,2 and 3 vessel disease respectively, whilst, in Group 2, percentages for the same severity subgroups were 11,31 and 57. Overall, exercise capacity was lower in Group 1 and 57% of these pts had an exercise time $\leq$6 mins (Bruce modified protocol). However, a large degree of overlap was observed and 10 pts (28%) of Group 2 had a similar exercise tolerance.

In the 49 pts of Group 1 we recorded 304 episodes of ST segment depression of which only 59 (19%) were associated with angina; 25 pts had both episodes with and without chest pain whilst 24 only had asymptomatic ischemia. The presence or absence of angina was not related to the severity of CAD and exercise tolerance. Therefore: (1) in a large percentage of pts with CSA ambulatory ECG monitoring detects frequent episodes of myocardial ischemia which are only partially related to the severity of CAD and impairment of coronary flow reserve. (2) the majority of these episodes are painless and some pts (25%) can be totally asymptomatic in spite of documented ischemia. (3) the occurrence of asymptomatic ischemia is not predicted by the severity of CAD nor by the degree of impairment of exercise tolerance.

THE VALUE OF THE ADMISSION ELECTROCARDIOGRAM TO PREDICT EFFECT OF THROMBOLYSIS ON INFARCT SIZE.

Frits Bär, M.D., Frank Vermeer, M.D., X Hanno Krauss, M.D., Jan Res, M.D., Maarten Simoons, M.D., F.A.C.C., Christoffel de Zwaan, M.D., Arnoud vd Laarse, PhD, Hein JJ Wellens, M.D., F.A.C.C. The Netherlands Interuniversity Cardiology Institute.

Predictive value of the ECG on admission was studied in 488/533 patients (pts) from a randomized trial of thrombolysis versus conventional therapy. All baseline data were similar in both groups. Presence or absence of Q's and sum of ST elevation (↑) (mm) were correlated with infarct size, estimated from cumulative myocardial alfa HBDH enzyme release.

Results: Overall, thrombolysis pts had significant lower infarct size (410U=30%) compared to control. Infarct size limitation was greatest in pts with Q's or high ST↑ (> 12 mm) in anterior (Ant) infarct (reduction of 820U=47% and 750U=39% respectively) and high ST↑ (> 6 mm) in inferior (Inf) infarct (reduction of 460U=36%). Nor in Ant or Inf infarct was infarct size influenced by streptokinase when the ECG showed the combination of low ST↑ and absence of Q's. The delay between onset of symptoms was an independent predictor of infarct size. In Ant and Inf infarct, control and thrombolysis pts had equal infarct size in presence of no Q + delay > 120' and low ST↑ + delay > 120'. The other pts showed lower infarct size after thrombolysis.

Conclusions: 1. Number of Q's and degree of ST↑ predict success of thrombolysis. 2. Thrombolysis does not reduce infarct size when the ECG on admission shows: no Q + low ST↑, independent of the delay between infarct and admission. 3. Infarct size also does not change when the combination: absence of Q's + delay > 120' or low ST↑ + delay > 120' is present. Those pts should not be treated with streptokinase.

THE HIGH PREVALENCE OF VENTRICULAR ARRHYTHMIAS IN THE 24 HOURS FOLLOWING REPERFUSION DOES NOT INDICATE A HIGH RISK FOR SUBSEQUENT SEVERE ARRHYTHMIAS.

Bojan Cercek, MD, Allan S. Lew, MD, Pierre Laramee, MD, P.K.Shah, MD, FACC, William Ganz, MD, CSc, FACC, and Thomas Peter, MD, FACC. Cedars-Sinai Medical Center, Los Angeles.

In 28 consecutive patients (Pts) with acute myocardial infarction who underwent early successful thrombolysis with intravenous streptokinase, a continuous 24-hr ECG was recorded immeadiately postreperfusion and on predischarge day (8±2).

During the 24 hr following reperfusion, all 28 Pts had isolated premature ventricular complexes (PVC) (median = 17 beats/hr, range: 1-176), 27 Pts (96%) had couplets (median = 1 couplet/hr, range: <1-24) and 25 Pts (89%) had runs of ≥3 ectopic beats (median = 67/24 hr, range 1-829).The number of beats in the longest run in any given Pt ranged from 4 - 7892 (median = 23) at a rate of 139±49 beats/min. PVCs were recorded throughout 24 hr in all patients. During the last 3 hr of recording significant arrhythmias tended to disappear with couplets being present in 6 Pts (21%) and runs in 5 Pts (18%) only.

Predischarge, 26 Pts (93%) had isolated PVCs (median = <1 beat /hr, range 1 - 39),only 3 Pts (11%) had <1 couplet/hr and 2 Pts (7%) had 1 short run of 3 and 6 ectopic beats respectively. There was no instance of ventricular fibrillation in either recording.

Conclusion: 1) Ventricular arrhythmias occur in most patients during the first 24 hr following early reperfusion. Couplets and runs of ventricular ectopic beats tend to cluster during the first hours after reperfusion and in most patients disappear over 24 hr. 2) At the time of discharge none of these patients developed severe ventricular arrhythmia.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #364/365
Cardiac Resuscitation

TWENTY FOUR HOUR SURVIVAL IN A CANINE MODEL COMPARING THREE METHODS OF MANUAL CARDIOPULMONARY RESUSCITATION.

Karl B. Kern, M.D., Alice B. Carter, Lee Showen, M.S., William D. Voorhees, Ph.D., Charles F. Babbs, M.D., Ph.D., Willis A. Tacker, M.D., Ph.D., Gordon A. Ewy, M.D., F.A.C.C., University of Arizona, Tucson, Arizona.

Two new methods of cardiopulmonary resuscitation (CPR), both suitable for basic life-support, have been reported to produce better hemodynamics than conventional CPR. However, whether either of these new methods will improve survival after cardiac arrest is unknown. Twenty-four hour survival and neurologic outcome were compared among 3 forms of manual CPR: standard at 60 compressions per min, high impulse compression (HIC) at 120/min, and interposed abdominal compression (IAC) at 60/min. Thirty mongrel dogs (20 to 32 kg) were equally divided among the 3 CPR methods. Following 3 minutes of ventricular fibrillation without intervention, CPR was performed for 17 minutes. No medications were given during the CPR period. Defibrillation was attempted at 20 minutes. Five standard CPR, 3 HIC CPR, and 2 IAC CPR animals survived 24-hours. There was no difference in 24 hour survival among the 3 types of CPR (χ^2=2.37, d.f.=2, p>0.1). Nine of the 10 survivors had totally normal neurologic function. Properly performed standard CPR appears as effective for survival and neurologic outcome as these two new modified versions of basic life-support.

SELF-ADHESIVE MONITOR/DEFIBRILLATION PADS:PREHOSPITAL USE
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The purpose of this study was to determine the relative efficacy of self-adhesive, dual function monitor/defibrillation pads vs. standard chest monitoring leads and defibrillation paddles in the management of prehospital cardiac arrest. Monitoring and defibrillation parameters, including incidence of loose-lead artifact which impaired rhythm interpretation, elapsed time from paramedic arrival to first shock, first shock conversion to organized rhythms, and overall termination of ventricular fibrillation (VF), were compared longitudinally in an urban paramedic system. For 14 months paramedics monitored through standard 3-lead chest electrodes (lead 2) and defibrillated with standard hand-held paddles. During the subsequent 12 months, self-adhesive monitor/defibrillation pads (R2 Corp., Skokie, Ill.) were employed for both functions. The pads performed significantly better with respect to a number of key parameters:

	Standard Leads/ Paddles	Self-Adhes. Pads	P value
Time from Arrival to First Shock (min.)	2.54+1.39	1.67+.87	<.001
First Shock Conversion to Organized Rhythm	18/67(27%)	17/34(50%)	< .05
Termination of VF:			
Per Patients	49/67(73%)	30/34(88%)	NS
Per Shocks	79/209(38%)	52/96(54%)	<.025

In addition, 19 of 73 patients (26%) monitored with standard leads received at least one shock when severe loose-lead artifact was misinterpreted as VF, while this happened with only 2 of 46 patients (4%, p<.01) when pads were used. Self-adhesive monitor/defibrillation pads are superior to standard chest leads and hand-held paddles in the management of prehospital cardiac arrest.

HYPOKALEMIA AFTER RESUSCITATION FROM VENTRICULAR FIBRILLATION.
David M. Salerno, Ph.D., M.D., FACC, Joseph Elsperger, CCPT, Peter Helseth, Vinaya Chepuri, Darryl Erlien, MS. Hennepin County Medical Center and Univ. of MN, Minneapolis, MN.

Hypokalemia has been reported in up to 1/3 of patients (pts) after resuscitation from out-of-hospital ventricular fibrillation (VF), being implicated as a predisposing condition. To test whether hypokalemia can occur secondary to VF and resuscitation, we induced VF in anesthetized dogs. After a period of VF, the dogs underwent ventilation and chest massage and finally electrical cardioversion. Arterial gases and serum potassium (K), sodium (Na), calcium (Ca), magnesium (Mg), phosphorus (P), and glucose (G) were obtained before and 7, 15, 30, 45, 60, 90, 120, and 180 min after VF.

Twenty dogs were resuscitated: 7 needed epinephrine (E) during resuscitation and 13 did not (no E). Five other dogs were anesthetized and instrumented but VF was not induced (control). The following K values (mmole/L) were obtained:

	n	Baseline	30	45	90	180
Control	(5)	3.7	3.5	3.4	3.4	3.6
All VF	(20	3.7	3.3	3.2*	3.3	3.5
VF (no E)	(13)	3.7	3.3	3.2*	3.3	3.5
VF (E)	(7)	3.8	3.5	3.3	3.3	--

*p<.005 by ANOVA from baseline

Changes in K were independent of pH. Serum G rose after VF (p<.001) but not in control dogs. Ca and Mg decreased after VF in both control and VF dogs. No changes in Na or P were observed.

Thus, after VF, K decreased independently of pH or exogenous E. These data suggest that the hypokalemia seen after VF in humans may develop following the event rather than exist as a predisposing condition as previously suggested.

AUTOMATED IMPEDANCE-BASED ENERGY ADJUSTMENT FOR TRANSTHORACIC DEFIBRILLATION AND CARDIOVERSION IN PATIENTS WITH HIGH TRANSTHORACIC IMPEDANCE: CONTINUED CLINICAL EXPERIENCE.
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We have previously shown that transthoracic impedance is a major determinant of ability to defibrillate when using low energy; low energy shocks, although safer, may be ineffective if transthoracic impedance is high. We have developed a method which identifies high transthoracic impedance (>70Ω) in advance of any shock and automatically compensates for the high impedance by doubling the operator-selected energy. Studies in animals and preliminary human experience, previously reported, were favorable. We have now used this automated approach in 29 high impedance (>70Ω) patients. In these high impedance patients the energy-adjusting defibrillator automatically increased operator-selected 100J shocks to 200J. The results of such energy-adjusted shocks were compared to the results of shocks given to an additional 30 high impedance patients using a standard defibrillator set at 100J. Some patients received several shocks. Results:

Rhythm	Defibrillator	Shocks: Succ/Total	% Success
At Fib	Standard	8/24]**	33%
	Automatic energy ↑	14/18]	78%
V Tach	Standard	11/19]*	58%
	Automatic energy ↑	19/19]	100%
V Fib	Standard	8/17	47%
	Automatic energy ↑	4/4	100%

*=p<.05. **=p<.01 by Chi-square test

Conclusion: Automated impedance-based energy adjustment improves the success of low-energy shocks for defibrillation and cardioversion by automatically increasing shock energy to compensate for high transthoracic impedance.

TWO FORMS OF "NEW" CPR: POSSIBLE ROLE OF A COMBINED THORACIC AND VASCULAR PUMP.
Karl B. Kern, M.D., Alice Carter, Lee Showen, M.S., William D. Voorhees, Ph.D., Charles F. Babbs, M.D., Ph.D., Willis A. Tacker, M.D., Ph.D., Gordon A. Ewy, M.D., F.A.C.C., University of Arizona, Tucson, AZ.

Simultaneous compression and ventilation (SCV) cardiopulmonary resuscitation (CPR) and vest CPR, were compared for survival and neurologic outcome. Twenty large (23 ± 0.7 kg) mongrel dogs were anesthetized with morphine and halothane. Ventricular fibrillation was electrically induced and one of the "new" CPR types begun after a 3 minute downtime. Simultaneous compression and ventilation CPR was performed with chest compressions at 40 times/min and simultaneous ventilations at 90 mm Hg. Vest CPR was performed using cyclic inflations at 50/min of both a pneumatic chest bladder (200 mm Hg) and an abdominal bladder (100 mm Hg), and with simultaneous ventilations (15 ml/kg). Cardiopulmonary resuscitation was performed for 17 minutes before defibrillation was attempted. Simultaneous compression and ventilation (SCV) produced significantly more coronary perfusion pressure at 2 and 7 min of CPR ($p<0.05$), but not at 12 or 17 min. Five of 10 SCV animals survived 24 hours versus only 1 of 10 vest animals ($p<0.05$, $\chi^2 = 3.81$ df= 1). Neurologic deficits were significantly less following SCV (54±16%) versus vest (91±9%; $p<0.05$). The differences between these two forms of "new" CPR may be due to a combination of a thoracic and a vascular pump affecting blood flow in SCV CPR.

ALTERATIONS IN ADENYLATE CYCLASE ACTIVITY AND α_1-RECEPTORS IN PATIENTS WITH VENTRICULAR TACHYCARDIA

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We measured adenylate cyclase (AC) activity and α_1-receptor properties in right ventricular septal biopsies from 8 patients (pts) undergoing electrophysiologic study for ventricular tachycardia (VT). None were on medication. Four pts with exercise-induced VT and 1 pt with septal VT, all with normal LV function, comprised group 1; 2 pts with a cardiomyopathy and 1 pt with myocarditis comprised group 2. AC activity (-basal) is expressed as pmol/mg protein/30min.

	Group 1	Group 2	P
1) NaF 10mM	5568±1739	1187±536	<.025
2) GppNHpp 0.1mM	3029±906	157±158	<.025
3) GppNHp 0.1mM +isoproterenol 1uM	4672±1263	1495±928	<.025
4) Isoproterenol 1uM	489±285	40±35	<.025
5) [3]-[2]	1643±529	1337±781	<.025

In 3 pts with normal LV function, the K_d for the α_1-selective antagonist ^{125}I-IBE-2254 was 379±95 pM and the maximum number of binding sites (Bmax) was 174±58 fmol/mg protein. In 1 pt with cardiomyopathy and 1 with myocarditis, values were 627 and 1200 pM and 670 and 644 fmol/mg protein, respectively. We conclude: 1) human myocardium contains high affinity low-capacity sites for α_1-receptors; 2) human AC, unlike rat but like the dog, is minimally responsive to 1uM (-)-isoproterenol, but increases markedly in the presence of 100uM GppNHp; and 3) abnormalities in AC activity and in α_1-receptors relate to the presence of underlying myocardial disease rather than to VT per se.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #364/365
Electrical Therapy and Detection of Arrhythmogenic States

MULTIPLE VS SINGLE PULSES TO AVOID VOLTAGE BREAKDOWN AND SHOCK-WAVE GENERATION WITH CATHETER MEDIATED ELECTRICAL PULSES.

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Electrical ablation of cardiac tissue can result in high pressure shock-waves. This phenomenon is signaled by breakdown in the voltage waveform as impedance rises during bubble formation at the electrode surface.

We used a high voltage, variable waveform modulator with a wide dynamic range to study whether multiple constant current, rectangular pulses (MP) with a shorter pulse width (PW) could deliver more energy before voltage breakdown than a single pulse (SP) at the same current but with a longer PW. All pulses were cathodal and delivered to a 6Fr 16mm^2 surface area Cu electrode in bovine blood. For SP's, PW was determined by the maximum possible pulse duration before voltage breakdown occurred. With MP's, the PW of individual component pulses was half of the SP PW at the corresponding current. MP duty factor was 10%. The number of pulses used for a MP burst was the maximum delivered before voltage breakdown occurred. The relation between SP and MP delivered energy before voltage breakdown follows:

Current(Amps)	6	8	10	12	14	16
SP:PW(μs)	320	180	140	96	72	62
SP:Energy(J)	0.9	0.9	1.1	1.1	1.1	1.2
MP:PW(μs)	160	90	70	48	36	31
MP:Energy(J)	2.4	3.0	2.8	2.5	2.4	5.2
MP:# of Pulses	5	6	5	4	4	9

Conclusion: For any given current SP's are less efficient in delivering energy than MP's with shorter PW's. MP's at very short PW's (31μs) yield the most energy before voltage breakdown. Eventually, however, even with MP's, voltage breakdown and shock-wave generation occur.

AUTOMATIC IMPLANTABLE DEFIBRILLATORS: TWO SEQUENTIAL PULSES ARE AS EFFECTIVE AS THREE.

Jerry L. Wessale, Ph.D; Joe D. Bourland, Ph.D; Gregory M. Ayers, B.S.; Willis A. Tacker, M.D., Ph.D; Michael J. Kallok, Ph.D; and Leslie A. Geddes, Ph.D., F.A.C.C. Biomedical Engineering Center, Purdue University, West Lafayette, IN

Use of 2 sequential shocks reduces the energy required for internal defibrillation by 60 to 80% in animals and man when 3 or 4 electrodes are used to create 2 separate current pathways in the heart. Whether use of 3 pulses will further reduce energy is not known, and is the subject of this study. In each of 6 mongrel dogs (mean body weight = 29.3 kg), ventricular defibrillation threshold energy was determined for 2 pulses and for 3 pulses delivered via epicardial electrodes. For 2 pulses, the sequence of current flowing through the heart was from 1) right to left and 2) anterior to posterior. For 3 pulses, the current sequence was: 1) apical-anterior to basal-posterior; 2) left to right; and 3) apical-posterior to basal-anterior. Total capacitance and duration of current flow were the same for 2 and 3 pulses. Pulse separation was 0.2 msec. Truncated-exponential waveforms with total durations of 1,2,5 and 10 msec and tilts of 50, 65, or 80% were tested. Mean energy for 3-pulse defibrillation was not less than for 2-pulse (p=0.01). For example, using pulses with total duration of 5 msec and tilts of 50%, the mean energy for 2-pulse defibrillation was 3.9± 1.0 joules (mean ± sd) and for 3-pulse was 4.8 ± 1.6 joules. Of 36 threshold pairs, energy for 3-pulses was greater in 24, the same in 8, and less in 4. For the electrode configuration tested, we conclude that defibrillation with 3 pulses does not reduce the energy requirement when compared to defibrillation with 2 pulses.

A COMPARATIVE ANALYSIS OF SIGNAL AVERAGING OF THE SURFACE QRS COMPLEX AND INTRACARDIAC ELECTRODE CATHETER RECORDING IN PATIENTS WITH VENTRICULAR TACHYCARDIA.

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Signal averaging (SA) of the surface QRS complex has been used to detect late potentials in patients (pts) with ventricular tachycardia (VT). However, these potentials may be more enhanced when recorded from a RV electrode due to its proximity to the source of delayed conduction. Thus, we performed a prospective study in 9 pts (59 ± 13 yrs) with sustained VT. All pts had SA of surface QRS (method [Me] I) and SA of an intracardiac electrogram utilizing an unipolar RV apical electrogram (Me II) during electrophysiologic studies. SA by the 2 (Me's) was performed within ≤ 24 hours of each other utilizing a band pass filter frequency of 25 to 250 Hz. The duration of the high frequency total QRS (HFTD), low amplitude signals (LAS) of <40μv and the RMS-voltage of the terminal 40 msec (V40) were determined for the 2 Me's. Results: There was a significant correlation between HFTD (r=.98,p<.001); LAS (r=.87,p<.005) and V40 (r=.89,p<.001) between the 2 Me's. The SA-parameters obtained by the 2 Me's are shown below.

Method	HFTD(ms)	LAS(ms)	V40(μv)	Noise
I	139±25	37±25	52±56	1.1±.6
II	148±26	31±28	36±30	1.3±.7

There was no significant difference between the 2 Me's. HFTD was >120 ms in 56% (Me I) vs 89% (Me II); LAS was > 32 ms in 33% (Me I) vs 22% (Me II) and V40 was <25 μv in 44% (Me I) vs 33% (Me II). In one pt Me II (HFTD=170 vs 105ms, LAS = 75 vs 33ms and V40 = 14 vs 40μv) provided more information relative to Me I. In conclusion: (1) SA of intracardiac electrograms correlates well with SA of surface QRS; (2) SA of intracardiac electrograms may provide additional information on SA parameters relative to surface QRS in some pts.

SELECTIVE PERCUTANEOUS CATHETER ABLATION OF THE RIGHT BUNDLE BRANCH IN PATIENTS WITH SUSTAINED BUNDLE BRANCH REENTRANT TACHYCARDIA

J Yeung Lai Wah, MB ChB, K Friday, MD, FACC, E Olson, MD, FACC, A Khan, MD, S Prabhu, MD and W Jackman, MD, University of Oklahoma and VA Medical Center, Oklahoma City, OK

Bundle branch reentry (BBR) has beer proposed as an uncommon mechanism for sustained ventricular tachycardia (VT). Creating right bundle branch (RB) block should eliminate the tachycardia and validate the mechanism. In 3 patients (pts) with intraventricular conduction delay (QRS = 180, 120 and 130 msec) and sustained VT exhibiting LBBB pattern, programmed ventricular stimulation (PVS) induced sustained VT similar in rate and morphology to the clinical VT. Induction of VT by PVS was reproducible and dependent upon critical V-H delay ($\geq$ 180, 220 and 210 msec). BBR was confirmed as each VT complex was preceded by retrograde H and' antegrade RB potentials and H-V and RB-V remained fixed despite changes in VT cycle length. Right ventricular extrastimuli during VT advanced the timing of subsequent QRS complexes only if the timing of the preceding H and RB potentials were advanced first, and terminated VT only by producing V-H block. The RB potential was recorded from an 8-electrode catheter with 3 mm spacing (center-to-center). In 2 pts, the RB potential was traced during VT until it merged with earliest ventricular activation near the apex. To selectively ablate the RB, the distal pair of electrodes was positioned over the proximal RB (10, 10 and 18 mm distal to the His bundle electrode) with H-RB = 10, 20 and 25 msec and RB-V = 50, 30 and 50 msec, respectively. One (2 pts) or two (1 pt) shocks of 300 joules were delivered between the coupled 2 distal catheter electrodes (cathode) and lateral/posterior chest paddle (anode). New RBBB was still present on ECG $\geq$ 5 days post-shock in all 3 pts. The first 2 pts were restudied at 1 week. The RB potential was absent and BBR complexes could not be induced during PVS despite achieving V-H intervals as long as 230 and 260 msec, respectively. We conclude: 1) selective RB ablation is feasible and safe, and 2) interruption of VT by proximal RB ablation confirms BBR mechanism.

DEMONSTRATION OF CATHETER ABLATIVE TECHNIQUE FOR CONTROL OF VENTRICULAR TACHYCARDIA DUE TO MACRO REENTRY WITHIN THE HIS-PURKINJE SYSTEM.

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Symptomatic ventricular tachycardia (VT) due to reentry within the His-Purkinje system (Re-HPS) has been reported to occur in 6% of patients with sustained monomorphic VT. This form of VT is also reportedly difficult to control with antiarrhythmic drugs. However, in contrast to other forms of VT, Re-HPS has a well defined circuit with accessible landmarks including the bundle branches (BBs). While catheter ablative technique may therefore be useful for Re-HPS it has never been previously demonstrated. This was attempted in a patient with VT and syncope found to have sustained Re-HPS. 200 J was delivered through the distal electrode of a quadripolar electrode catheter (with proximal electrode pair recording HB) to a posterior chest paddle. EKG recorded new RBBB but intact AV conduction. Re-HPS was no longer inducible immediately and 3 days post ablation. Syncope or VT has not recurred during one year follow up.

We conclude that: 1) Selective RB ablation using electrode catheter technique is possible and is a potential therapy for VT due to sustained Re-HPS. 2) In such cases RB ablation is preferable to HB ablation because complete heart block is not required for treatment. 3) Moreover, since the reentrant circuit may not include the more proximal HB, HB ablation, in contrast to RB ablation, may not prevent Re-HPS.

COMPARISON OF RESETTING AND TERMINATION OF VENTRICULAR TACHYCARDIA WITH PROGRAMMED EXTRASTIMULI.

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Both resetting and termination of ventricular tachycardia (VT) require that the paced impulse reaches the VT origin at a critical time. Single ventricular extrastimuli (SVE) were delivered during 81 distinct VT from the RV - apex. Double ventricular extrastimuli (DVE) (with the coupling interval of the first set to cause no resetting) were delivered in 34 VT. In total, 60 VT were reset and 21 terminated. Resetting was more frequent than termination with both SVE (56% vs. 9%; $p<.001$) and DVE (100% vs 41%; $p<.001$). Resetting preceded termination in 19 of 21 VT, thus termination occurred in only 2 VT without prior reset. The ability to reset or terminate VT was not related to VT morphology, axis, or site of origin determined by LV mapping. Compared to VT requiring DVE for resetting, VT reset with SVE demonstrated left bundle branch block QRS more frequently than right bundle branch block (53% vs 25%, $p<.03$), a shorter activation time to the RV apex during VT (62±48 ms vs 98±60 ms, $p<.03$), and a longer VT cycle length (382±60 vs 338±49 ms; $p<.02$). A similar comparison for VT termination, demonstrated that only a longer VT cycle length (399±59 vs 346±39; $p<.03$) significantly distinguished VT terminated by an SVE from VT requiring DVE for termination. We conclude: 1) Both resetting and termination of VT by SVE, as compared to DVE, are faciliated by a longer VT cycle length and, in the case of resetting alone, a shorter activation time to the pacing site during VT; 2) The ability to reset VT is a marker for the ability to terminate VT with programmed extrastimuli and may select patients in whom pacing therapy may be considered.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #157
Dynamics of Left Ventricular Diastolic Filling

LOAD-DEPENDENT RELAXATION IN THE INTACT LEFT VENTRICLE.

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In isolated heart muscle preparations an abrupt increase in load during the latter half of contraction (at a time when there is little if any potential to develop additional force) causes a premature and more rapid relaxation; this load-dependent relaxation (LDR) characterizes relaxation in myocardium with normal sarcoplasmic reticulum. The purpose of this study was to evaluate the presence of this phenomenon in the intact left ventricle (LV). Using a microcomputer controlled servo-pump attached to the LV apex (5 anesthetized dogs), we studied the effects of 6 ml volume increments (quick stretch or volume steps) on LV pressure transients (micromanometer). Each step (given at 30 msec intervals throughout systole) was carried out in a single beat with 20 control beats between step beats. In ejecting beats (n=23) an early systolic step near aortic valve opening caused an increased duration of contraction-relaxation (average 10 msec); however, a late step near aortic valve closure caused an early onset of relaxation and shorter duration (average 23 msec). In "isovolumic beats" (single-beat aortic occlusion plus step, n=47), results were similar; steps after the first 1/3 of systole caused early relaxation with maximum effect at peak pressure: duration fell by 13% (average 28 msec) and peak (-)dP/dt increased by 75% (average 1710 to 2975 mmHg/sec).

The observed premature and rapid relaxation with late systolic volume steps confirms a form of LDR in the intact LV. Hemodynamic steps (i.e. reflected pressure waves and other late systolic events) and/or alterations in the mechanisms underlying LDR (i.e. abnormal sarcoplasmic reticulum) may be responsible for changes in relaxation in normal and diseased hearts.

VARIABLE RELATIONSHIPS OF MITRAL VALVE MOTION AND FLOW

Pamela S. Douglas, M.D., F.A.C.C., Barbara A. Berko, M.D., Alfred Ioli, Nathaniel Reichek, M.D., U of Penn, Phila. PA

To examine the relationship between transmitral flow and diastolic mitral valve (MV) motion, we compared MV echograms with pulsed Doppler recordings of LV inflow in 44 subjects. There were 17 normals (NL), 15 hypertensives (HBP, all normal LV function) and 12 cardiomyopathics (CM, EF 20±6%). Echograms were analyzed for maximal early and late diastolic leaflet separations, their ratio and early anterior leaflet opening and closing slopes. Flow profiles were analyzed for peak early and late velocities, their ratio and early flow acceleration and deceleration. Volume flow was estimated as leaflet separation times velocity.

Corresponding MV leaflet separations and peak velocities were poorly correlated. Early flow decceleration and MV E-F slope were weakly related (r=.49), while flow acceleration and rate of leaflet opening were not. In CM, E and A point MV leaflet separations (E-E, A-A) and early flow velocity (E) were reduced. In HBP, E-E was reduced and late flow velocity (A) was increased ($p<.01$). Early volume flows were decreased in CM and HBP, and late flow was increased in HBP ($p<.05$). The ratios of early to late velocities (E/A) and volumes were smaller in HBP ($p<.05$), although the ratios of MV leaflet separations were similar in all subjects. (*$p<.01$ vNL,HBP;**$p<.05$ vNL,CM;†$p<.05$ vNL)

	E-E	A-A	E-E/A-A	E	A	E/A
NL	3.18	2.31	1.41	61.8	40.1	1.61
HBP	2.83†	2.34	1.28	52.2	52.5**	1.04†
CM	2.19*	1.76*	1.24	48.4†	41.8	1.38

Despite qualitative similarities, MV motion and flow are poorly related and are affected differently in CM, with reduced leaflet excursion throughout diastole, and in HBP, with increased peak velocity and volume of atrial filling. Alterations of volume flow may be due to changes in MV orifice size, flow velocity or both.

PARTIALLY VERSUS FULLY CONSTRAINED MODELS OF THE DIASTOLIC LEFT VENTRICLE

Chester M. Boltwood, Jr., M.D., Pravin M. Shah, M.D., F.A.C.C. Wadsworth VA/UCLA, Los Angeles, CA.

A realistic model of the diastolic LV should account for extramural as well as intracavitary forces. The pressure outside the LV septum is RVDP (diastolic pressure). The pressure exerted by the pericardium on the LV free wall (PP) is controversial, but presumably satisfies $0 \leq PP \leq RVDP$. Assuming that the septum carries 1/3 of the total LV external surface, we therefore estimated the average transmural LVDPtm as (LVDP - 1/3 RVDP) (partially constrained, PC, ie. PP=0), or as (LVDP - RVDP) (fully constrained, FC, ie. PP=RVDP). In 6 coronary pts without Q waves frame-by-frame angiographic LV volume (V) was related to micromanometer LVDPtm after nitroglycerin (NTG) and subsequent volume challenge (VC). Curve shifts were assessed by regression in a dummy variable S (0 for NTG, 1 for VC). Unstressed volume Vo was obtained by extrapolating to zero LVDPtm, and compared to end-systolic Ves.

Results: From NTG to VC RVEDP rose 8±2 to 19±11 mm Hg ($p<0.05$), LVEDP 12±2 to 32±6 mm Hg ($p<0.001$), and LV pressure decay $T_{\frac{1}{2}}$ 37±7 to 40±6 ms ($p=0.053$). PC S coefficient was 6.5±3.3 mm while FC was 2.4±2.1 mm Hg ($p<0.05$). PC Vo was -37±51 ml while FC was 68±20 ml ($p<0.01$), and FC Vo was always > Ves of 34±10 ml ($p<0.01$).

Conclusions: The PC model predicts a Vo which is non-physiologically small or even negative. The FC model always satisfies Vo > Ves, which may be physiologic if elastic recoil occurs during early diastole. Diastolic pressure-volume curve shifts induced by volume manipulations were much smaller in the FC than PC model, but not wholly eliminated. Thus, the relation PP ≅ RVDP suggested in recent literature may be accurate, but other factors besides constraint may contribute to residual pressure-volume curve shifts.

TORSIONAL DEFORMATION OF THE HUMAN LEFT VENTRICLE: ALTERATIONS DURING CARDIAC ALLOGRAFT REJECTION.

David E. Hansen, M.D., George T. Daughters, M.A., Edwin L. Alderman, M.D., F.A.C.C., John C. Baldwin, M.D., Philip E. Oyer, M.D., Neil B. Ingels, Ph.D., Edward B. Stinson, M.D., D. Craig Miller, M.D., F.A.C.C., Stanford University, Stanford, CA.

To investigate LV systolic torsion and diastolic recoil in man, serial measurements were made in 7 heart transplant recipients over a span of 8 weeks following surgery and related to the presence or absence of biopsy-proven rejection. Measurements are based on 12 tantalum markers implanted in the basal, equatorial, and apical portions of the anterior, inferior, and lateral walls. The torsional deformation characteristics relative to an internal reference system were calculated by computer-aided analysis of the 3-dimensional marker motion on biplane cinefluoroscopic recordings. Comparisons of measurements before, during, and following recovery from 9 rejection episodes enabled assessment of the effects of an acute reversible myopathy on LV torsion and recoil. Compared to pre-rejection values, the amplitude of torsion in the maximally deforming segment (TDmax) decreased during acute rejection with myocyte necrosis from 20.1±5.6 to 17.1±5.5° ($p<0.001$). Peak systolic torsion and diastolic recoil rates were unchanged at 178±92 vs. 147±56 (NS) and 209±93 vs. 191±73 deg/sec (NS) respectively. The segmental hierarchy of the amplitude of torsion was consistently maintained during rejection. Over a wide range of values in 49 studies, no correlation between TDmax and stroke volume, peak coiling rate and velocity of fiber shortening, and peak recoil rate and maximum LV filling velocity were demonstrated. We conclude that during acute rejection: 1) The amplitude of LV torsion decreases without altering LV coiling or recoil rates; 2) The regional hierarchy of torsional deformation is preserved; and 3) LV systolic torsion and diastolic recoil may be functionally dissociated from segmental shortening and filling of the LV cavity.

ASSESSMENT OF DIASTOLIC PRESSURE-VOLUME RELATION IN THE INTACT LEFT VENTRICLE BY PULSED-DOPPLER ECHOCARDIOGRAPHY.

Robert D. Aronoff, M.D., William A. Zoghbi, M.D., Roxann Rokey, M.D., Roberto Bolli, M.D., Miguel A. Quinones, M.D., F.A.C.C., Baylor College of Medicine, Houston, TX

Assessment of LV diastolic pressure (P)-volume (V) has previously required angiography and this has limited the capacity for serial observations and beat by beat analysis. We have shown that mitral annulus (MA) flow, derived as the product of flow velocity by Doppler and the annulus area represents a measure of LV filling rate. Accordingly, Doppler MA flow curves were integrated and combined with end-diastolic volumes by 2-dimensional echo in 30 patients to derive diastolic volume curves which qualitatively resembled those obtained by angiography. In 5 patients, simultaneous recordings of MA flow velocity and LVP (micromanometers) were used to construct diastolic P-V curves which were of high resolution in all patients. Viscoelastic properties were readily appreciable as deviations from an idealized exponential curve. The modulus of chamber stiffness (K) was determined as the slope of dP/dV vs P during the curvilinear segment of the P-V curve. This method was applied in 5 open-chest dogs to examine diastolic P-V relations during acute ischemia induced by <10 min coronary occlusions (n=10). A readily appreciable shift upward and to the left was seen in the P-V curves with ischemia. Flattening of the curves during diastole and prominent viscoelastic effect resulted in non-linear dP/dV-P relations (n=5). In cycles with a linear dP/dV-P relation (n=5), a significant increase in K was observed from control ($.37 \pm .22$ ml^{-1}) to ischemia ($.85 \pm .54$; $p<.05$). Thus, combined use of Doppler-MA flow velocity and LVP provides a new method of assessment of diastolic pressure- volume relations on a beat by beat basis which is highly suitable for acute and serial observations.

ASYNCHRONY IN REGIONAL FILLING DYNAMICS AS A CONSEQUENCE OF UNCOORDINATED SEGMENTAL CONTRACTION DURING TRANSLUMINAL CORONARY OCCLUSION.

Federico Piscione, MD, Patrick W. Serruys, MD. Thoraxcenter, Rotterdam, the Netherlands.

The effects of brief periods of a major coronary artery occlusion on the global (GPFR) and regional (RPFR) peak filling rates were studied in 14 patients during angioplasty. None had had a previous myocardial infarction. High-fidelity left ventricular pressure and volume (angiography) measurements were obtained before,20 and 50 seconds after the onset of transluminal coronary occlusion (TCO) and shortly after the last TCO. Segmental wall motion was analyzed frame by frame along 20 hemiaxes. GPFR decreased significantly both after 20 (-25%; $p < .05$) and 50 seconds (-24%;$p < .05$). The term $\Sigma \Delta t_1$ was defined as the sum of the absolute values of the time differences between the occurrence of GPFR and the peak velocity of segmental outward displacement, which reflects the RPFR, in 20 segments. This parameter increased significantly during both periods of TCO (by 64%; $p<.005$ and by 54%; $p<.005$ respectively) thus indicating an asynchrony in the occurrence of RPFR. Simultaneously the sum of time intervals between the aortic valve closure (end-systole) and the occurrence of peak segmental shortening, $\Sigma \Delta t_2$, measured in the 20 segments,increased to a similar extent, thus demonstrating an asynchrony in segmental contraction. We found a significant, negative correlation between GPFR and both $\Sigma \Delta t_1$ and $\Sigma \Delta t_2$ ($r = -.68$; $p<.0001$ and $r=-.73$; $p<0001$ respectively). In addition a significant correlation existing between $\Sigma \Delta t_1$ and $\Sigma \Delta t_2$ ($r=.66$;$p < .0001$) indicates that the asynchrony in RPFR reflects an asynchronous segmental contraction and thus, a decrease in GPFR occurring early during acute ischemia, actually demonstrates an altered myocardial contraction.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #157
Experimental Hypertension

BETA ADRENERGIC RECEPTORS AFTER HYPERTROPHY AND ITS REVERSAL IN THE RENAL HYPERTENSIVE RAT

Jadwiga Szlachcic, M.D., Julio F. Tubau, M.D., Barry Massie, M.D., F.A.C.C., Wanda Woloszyn, Norman Honbo and Joel S. Karliner, M.D., F.A.C.C. Cardiology Section, VAMC and UCSF San Francisco, California.

There is evidence that β-adrenergic receptor changes accompany the development of hypertrophy due to pressure overload, but few data exist regarding β-receptor properties after reversal of long-standing hypertrophy. Thus, we used the 1 clip-2 kidney Goldblatt model to produce LV hypertrophy. Treatment with α-methyldopa (MD), 400 mg/kg/day, diltiazem (DL), 60mg/kg/day or placebo (PL) was was started after 12 weeks of hypertension and continued for 3 months. Sham operated (SH) animals were used as controls. Saturation radioligand binding isotherms were performed in cardiac particulate preparations using ^{125}I-iodcyanopindolol.

	BP (mmHg)	LV weight (gm)	Kd (pM)	Bmax (fmol/mg DNA)
SH (n=4)	119±19	1.02±.108	162±47	585±46
PL (n=3)	176±15**	1.50±26**	93±20	924±14**
MD (n=4)	134±12*##	1.12±.20**	116±10	541±78##
DL (n=4)	145±12##	1.27±.14*#	147±31	649±75##

* p<.05, **p<.01 vs SH, #p<.05, ##p<.01 vs PL

We conclude 1) β-receptor density is increased after 6 months of sustained hypertension; 2) virtually complete reversal of hypertrophy by the centrally acting sympatholytic agent α-methyldopa or partial reversal by the calcium entry blocker diltiazem are both accompanied by a return of β-receptor numbers to control levels.

DECREASED ENDOTHELIUM-DEPENDENT RELAXATIONS TO ACETYLCHOLINE IN THE AORTA OF HYPERTENSIVE DAHL RATS.

Thomas F. Lüscher, M.D., Leopoldo Raij, M.D. and Paul M. Vanhoutte, M.D., Department of Physiology, Mayo Clinic, Rochester, Minnesota.

The endothelium may play an important role in the local control of vascular smooth muscle. In hypertension the endothelium changes morphologically and functionally. Endothelium-dependent relaxations to acetylcholine (ACh) are decreased in spontaneously hypertensive rats. In the present study endothelium-dependent relaxations were investigated in a different model of hypertension. Salt-sensitive and salt-resistant Dahl rats were given 8% NaCl for 8 weeks. At the end of this period systolic blood pressure averaged 183 ± 7 mmHg in salt-sensitive (n=6) and 125 ± 3 mmHg in salt-resistant animals (n=4; $P < 0.05$). Rings with or without endothelium, of thoracic aorta, from both strains were suspended in organ chambers for isometric tension recording. In both groups ACh (10^{-9}-10^{-4}M) caused relaxations in rings with but not in those without endothelium. However, relaxations were significantly depressed in salt-sensitive as compared to salt-resistant rats (IC50: 5.6×10^{-7}M and 4.2×10^{-8}M: $P < 0.05$). In the latter, the maximal relaxations occurred at lower concentrations (10^{-6}M) and were more pronounced (100%) than in salt-sensitive rats (1.5×10^{-5}M; 78 ± 9%). Relaxations to sodium nitroprusside did not differ in aortas of the two strains. Thus, the decreased endothelium-dependent relaxations to ACh in hypertensive Dahl rats may be due to decreased release of and/or sensitivity of the smooth muscle to endothelium-derived relaxing factor(s) rather than structural changes occurring in hypertension. (Supported in part by NIH grant HL 31183.)

DISSOCIATION OF ADRENERGIC RECEPTOR DENSITY FROM RESPONSES TO ADRENERGIC AGENTS IN A BABOON MODEL OF HYPERTENSION

Marilyn L.Hurwitz, M.Sc. and Clive Rosendorff, M.D., Ph.D. F.A.C.C., MRC/University Circulation Research Unit and Departments of Physiology and Medicine, University of the Witwatersrand Medical School, Johannesburg, South Africa.

There have been some reports of increased vascular responsiveness to α_1-adrenoceptor agonists and reduced myocardial sensitivity to β-adrenoceptor agonists in human and experimental hypertension. To study the mechanism of these effects we measured α_1 and β adrenoceptor (R) number (Bmax) by radioligand binding assay, and the hemodynamic responses to phenylephrine (PE, α_1-agonist), prazosin (PRAZ, α_1-antagonist), isoproterenol (ISO, β-agonist) and propranolol (PROP, β-antagonist) in the 2-kidney Grollman model of hypertension in the baboon (HT, n=8) vs sham-operated controls (C, n=8). In HT vascular smooth muscle α_1-R Bmax was increased (562±1 vs 134±1 fmol/mg protein, $P<0.05$) and myocardial β-R Bmax was decreased (44±5 vs 119±3 fmol/mg protein, $P<0.005$). Dose-response curves of PE (10^{-8}-10^{-2}M) vs mean arterial blood pressure showed no difference between HT ($ED_{50}=5.0 \times 10^{-4}$M) and C ($ED_{50}=5.8 \times 10^{-4}$M). Pretreatment with PRAZ failed to show up any difference between HT and C ($ED_{50}=2.8 \times 10^{-3}$ M and 3.3×10^{-3}M). On the other hand, ISO (10^{-8}-10^{-3}M) vs heart rate was significantly shifted to the right in HT ($ED_{50}=2.3 \times 10^{-6}$M) compared to C ($ED_{50}=7.5 \times 10^{-7}$M) consistent with the lower myocardial β-R Bmax; but this difference disappeared after PROP ($ED_{50}=7.3 \times 10^{-6}$M vs 6.5×10^{-6} M). We conclude that, in this animal model of hypertension, there is a dissociation of adrenergic receptor density from adrenergic drug responsiveness.

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β-ADRENOCEPTOR DENSITY ON ADIPOSE TISSUE-AN INDICATOR FOR CARDIAC β-ADRENOCEPTOR DENSITY IN SPONTANEOUSLY HYPERTENSIVE RATS.

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A reduction in β-adrenergic receptor density has been reported in hypertensive myocardium. To determine the correlation among β-adrenergic receptor density in peripheral lymphocytes, fat and ventricular myocardium, we simultaneously sampled lymphocytes, fat and myocardium from 7 spontaneously hypertensive rats(SHR)(70-100 days old). Receptor density was assessed by [I-125] cyanopindolol (ICYP) binding normalized to mg protein, and it correlated highly in fat and myocardium (r=0.92). However, the correlation between lymphocytes and myocardium was very poor(r=0.28). ICYP Kd was not significantly different among 3 groups(171 pM in lymphocytes, 133pM in fat and 234 pM in myocardium). Competitive binding for propranolol and β-1 selective blocker, metoprolol was also examined in these tissues. Antagonist inhibition curve showed similar pattern in fat and myocardium, but it was different in lymphocytes. These results suggest that adipose tissue could serve as an indicator for β-adrenoceptor density of cardiac tissue in SHR. However, lymphocyte had binding characteristics of β-2 subclass and it might not be available as an indicator for cardiac β-adrenoceptor density in hypertension.

EFFECTS OF EXERCISE ON THE CORONARY CIRCULATION OF CONSCIOUS HYPERTENSIVE RATS.

Pierre A. Wicker, M.D. and Robert C. Tarazi, M.D., F.A.C.C., Cleveland Clinic Foundation, Cleveland, Ohio.

Exercise is known to promote myocardial vascularity. We therefore, studied whether it could prevent coronary abnormalities of hypertensive left ventricular (LV) hypertrophy. Female Sprague-Dawley 1C-2K Goldblatt hypertensive rats (RHR) and their appropriate controls (Sham-SH), were either made to swim (RHR-SW, SH-SW) or kept sedentary (RHR-SED, SH-SE D) for 9 weeks. Minimal coronary resistance after carbochrome (total LVCR/LV mmHg/ml/min), an index of functional cross sectional area (CSA) of coronary resistance vessels, was determined in conscious rats by microspheres. Results (m ± SD) (n=12 in all groups):

GROUP	SH-SED	SH-SW	RHR-SED	RHR-SW
MAP (mmHg)	111±9	111±18	179±30	186±10
LVW/BW (mg/g)	2.3±0.2	2.7±0.3†	3.6±0.5	4.1±0.6†
LVCR/LV	10±3.3	7.3±1.4†	9.4±1.4	9.9±2.8

† SW vs SED, p<0.02.

Exercise increased functional coronary CSA in normotensive rats only. This beneficial effect did not occur in hypertension, probably because of the functional or structural changes in the coronary vessels of RHR.

MYOCARDIAL BIOCHEMICAL, CONTRACTILE AND ELECTRICAL PERFORMANCE FOLLOWING IMPOSITION OF HYPERTENSION IN YOUNG AND OLD RATS.

Joseph M. Capasso, PH.D., Ashwani Malhotra, PH.D., James Scheuer, M.D., F.A.C.C. and Edmund H. Sonnenblick, M.D., F.A.C.C., Albert Einstein College of Medicine, New York.

To study the effects of hypertension on the biochemical, contractile and electrical performance of aged myocardium male rats at 2-, 7-, 12-, and 17-mo of age were made hypertensive by left renal artery constriction. Ten weeks after the onset of hypertension left ventricular papillary muscles were isolated from these four age groups at 5-, 10-, 15-, and 20-mo of age. Mechanical performance and transmembrane electrical events were recorded simultaneously. Contractile protein enzyme activity was determined in the same hearts. Control groups revealed a decrease in mechanical, electrical and biochemical performance as a function of age. Hypertensive groups revealed myocardial hypertrophy resulting from the pressure overload which was approximately 50% in the 5-, and 15-mo-old animals and approximately 10% in the 20-mo-old animals. Adaptation to the stress of hypertension was observed in each age group and was revealed as prolongation of mechanical and electrical timing parameters and depression of the load-velocity relation and contractile protein enzyme activity. The biochemical, electrical and mechanical response of 2-mo-old animals to the stress of hypertension was significantly greater than that exhibited by the 17-mo-old animals. These biochemical and electrophysiological alterations may help to explain the contractile modification seen with the combination of aging and hypertension. The inability to compensate to the stress of hypertension may play an important role in heart failure in the aged, hypertensive population.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #267
Epidemiology: Risk Factors

LINOLEIC ACID AND CORONARY HEART DISEASE (CHD).

David A. Wood, M.Sc., M.R.C.P., Susan M. Butler, Ph.D., Rudolph A. Riemersma, Ph.D., Cecilia C. A. MacIntyre,M.Sc., Robert A. Elton, Ph.D. and Professor M. F. Oliver, M.D., F.R.C.P.
Cardiovascular Research Unit, University of Edinburgh, Edinburgh, Scotland, U.K.

The relationship between the essential fatty acid linoleic acid (LA) measured in adipose tissue and the risk of CHD has been investigated in a case control study. 88 cases of acute myocardial infarction (AMI) in men (≤55 years) with no history of CHD were studied. 107 new cases of angina pectoris (AP) with no reported history of CHD, were identified by the WHO chest pain questionnaire in a postal survey of a random sample of 6000 men (35-55 years) and studied with 393 asymptomatic healthy controls drawn from the same random sample.

The relative risks of CHD by quintiles of adipose tissue LA distribution in the controls are given in the table (*p<0.05).

L.A. (Medians %)	7.1%	8.1%	9.3%	10.6%	13.1%
AMI	3.3*	3.2*	2.7*	0.75	1.0
AP	3.2*	2.6*	2.4*	1.5	1.0

There is a strong correlation between dietary LA and adipose LA (r=0.58) and this study provides evidence of an inverse relationship between LA and the risk of CHD for individuals.

MARINE LIPID CONCENTRATE REDUCES CORONARY RISK FACTORS: DOUBLE BLIND COMPARISON WITH OLIVE OIL.

Michael H. Davidson, M.D., Philip R. Liebson, M.D.,F.A.C.C., John D. Bagdade M.D., Joseph V. Messer, M.D.,F.A.C.C., and James A. Schoenberger, M.D. F.A.C.C. Rush-Medical College, Chicago, IL.

Dietary omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexanoic acid have been shown to lower plasma lipids and reduce blood pressure. This study examined the efficacy of a marine lipid concentrate (MaxEPA®) in lowering plasma lipids and blood pressure in a double blind randomized study in patients with documented coronary artery disease. Thirty patients with elevated cholesterol levels were randomized into two groups, each receiving 20 capsules of either MaxEPA® or olive oil. The total daily dose of EPA was 3.6 grams. Baseline total cholesterol (TC), HDL-cholesterol (HDL), triglycerides (TG) and resting systolic (SBP) and diastolic (DBP) blood pressure measurements were repeated after 30 days of treatment. The results were as follows:

	TC	HDL	TG	SBP	DBP
MaxEPA® pre	326	47.2	237	137	87
post	285	49.4	142	128	80
	p<.025	(NS)	p<.005	p<.005	p<01
Olive oil pre	291	45.8	270	146.4	88.1
post	283	45.4	254	147.2	84.3
	(NS)	(NS)	(NS)	(NS)	(NS)

The TC/HDL ratio fell 17% in the MaxEPA® group (p<.005) and only 4% (NS) in the olive oil group. Compliance as determined by capsule counting was excellent and neither group reported significant adverse reactions. In conclusion, marine lipid concentrate dietary supplementation is an effective means of utilizing omega-3 fatty acids to lower plasma lipids, especially triglyceride rich lipoproteins and lowers blood pressure in motivated patients with coronary artery disease.

HIGH SERUM CHOLESTEROL AND ATHEROSCLEROSIS DO NOT CONTRIBUTE TO INCREASED ARTERIAL STIFFENING WITH AGE.

Michael F. O'Rourke, MD, FACC, Alberto P. Avolio, PhD, Kathy Clyde, Leon Simons, MD, Kenneth Ho and Donald Bains. St. Vincent's Hospital, Sydney, Australia.

Accelerated arterial stiffening with age is often attributed to atherosclerosis. To test this concept, aortic pulse wave velocity (PWV), an accepted index of arterial stiffness, was measured non-invasively in two population groups with different levels of serum cholesterol and different prevalence of atherosclerosis:- 53 subjects (aged 6-71 years) with heterozygous familial hypercholesterolemia (FH) and 53 Seventh Day Adventist subjects (aged 18-76 years) who followed a strict vegetarian diet (VD). Each group was compared with a group of 53 control subjects matched for age and mean arterial pressure (C1 and C2 respectively). Regression equations were obtained for PWV (Y, cm/sec) and age (X, years). Results were as follows :

	Serum Cholesterol(mmol/L)	PWV
FH	8.32 SE 0.30 (P<0.001)	Y=7.6X+460;r=0.67;P<0.001
C1	5.64 SE 0.19	Y=8.4X+535;r=0.39;P<0.05
VD	4.90 SE 0.22 (P<0.005)	Y=10.8X+387;r=0.59;P<0.01
C2	5.68 SE 0.13	Y=7.8X+614;r=0.30;P<0.05

Aortic PWV increased with age in a similar fashion in the FH and VD subjects and there was no significant difference compared to controls. Serum cholesterol, however, was markedly different (P<0.0001). These findings complement previous studies on Australian and Chinese subjects which showed that arterial stiffening with age is related to arterial pressure and salt intake but not to levels of serum cholesterol nor to prevalence of atherosclerosis.

APOLIPOPROTEINS A-I AND B IN CHILDREN ARE BETTER PREDICTORS OF PATERNAL MYOCARDIAL INFARCTION THAN ARE LIPOPROTEIN CHOLESTEROLS.

David S. Freedman, Ph.D., Sathanur R. Srinivasan, Ph.D., Charles L. Shear, Dr.P.H., Larry S. Webber, Ph.D., and Gerald S. Berenson, M.D., F.A.C.C. National Research and Demonstration Center--Arteriosclerosis, Louisiana State University Medical Center, New Orleans, LA.

Clinical studies indicate the protein components of lipoproteins are good predictors of coronary artery disease. Associations of childhood levels of apolipoproteins A-I and B (apo A-I, apo B) to reported histories of early (before age 50) paternal myocardial infarction (MI) were therefore assessed in a community-wide, biracial examination of 5- to 17-year-olds. Offspring whose father reported MI (n=141, 5.7%) had lower levels of both apo A-I (136.6 vs 140.8 mg/dl, p=0.02) and the ratio of low density lipoprotein cholesterol (LDL-C) to apo B (1.09 vs 1.11 mg/dl, p=0.001), along with higher levels of apo B/apo A-I (0.65 vs 0.61 mg/dl, p=0.01) than did children without paternal MIs. Associations were evident in both whites and blacks, and in boys and girls independently of age, obesity, smoking, alcohol intake and oral contraceptive use. Fathers of children at high risk (high apo B/apo A-I, low LDL-C/apo B) were 3.5 times more likely to have had an MI than were fathers of low-risk children. In contrast, offspring with paternal MIs did not have significantly different levels of total cholesterol, or high density lipoprotein cholesterol than did children without paternal MIs. Apolipoproteins appear to be better predictors of future MI than are levels of total cholesterol and lipoprotein cholesterol fractions. Optimal assessment of cardiovascular disease risk should therefore include apo A-I and apo B measurements.

SOTALOL FOR THE TREATMENT OF PATIENTS WITH DOCUMENTED VENTRICULAR FIBRILLATION: ELECTROPHYSIOLOGICAL AND ANTIARRHYTHMIC PROPERTIES

Johannes Brachmann, M.D., Jochen Senges, M.D., Ioannis Rizos, M.D., Claus Schmitt, M.D., Isaac Aidonidis, M.D., Wolfgang Kübler, M.D., F.A.C.C., Department of Cardiology, University of Heidelberg, West Germany.

Twenty-three resuscitated patients (P) with clinically documented ventricular fibrillation (VF) and inducible malignant ventricular tachyarrhythmias were selected for investigation of the acute effects of sotalol (SOT) using programmed right ventricular stimulation; sotalol (1.5 mg/kg iv) resulted in plasma concentration of 2.3±0.44 µg/ml. The following parameters were determined: 1) inducible ventricular tachyarrhythmias: VF and sustained ventricular tachycardia (S-VT); non-sustained ventricular tachycardia (NS-VT); 2) electrophysiological parameters: V-ERP, ventricular effective refractory period; QRS, QRS duration; QTc, corrected QT interval.
Results: SOT vs. control (CON), *p<0.05

	VF	S-VT	NS-VT	All	V-ERP(ms)	QRS(ms)	QTc(ms)
CON	5P	12P	6P	23P	244±12	106±13	415±22
SOT	3P	3P	4P	10P*	283±14*	108±16	452±34*

Eight P receiving long-term oral sotalol treatment (340-480 mg/d) had no symptomatic recurrence for 11±6 months. Conclusion: In approximately half of the resuscitated P with documented VF, inducibility and clinical occurrence of malignant ventricular tachyarrhythmias are suppressed by sotalol; the electrophysiological effects can be explained by its class III antiarrhythmic properties.

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PREDICTION OF EJECTION FRACTION USING ROUTINE CHEST X-RAY AND ECG: A PRACTICAL NON-INVASIVE METHOD BASED ON THE CONCEPT OF VOLUME/MASS RELATIONSHIP.

Miodrag Ostojic, MD, James B. Young, MD, FACC, Srecko Nedeljkovic, MD, William H.Spencer III, MD, FACC, William L. Winters, MD, FACC, Craig M. Pratt, MD, FACC, Miquel A. Quinones,MD,FACC, Milosav Milosevic,MD, Univ of Belgrade, YU, and Baylor College of Medicine, Houston, TX.

An accurate, rapid, inexpensive, non-invasive method of determining LV ejection fraction(EF) is necessary to evaluate LV function in epidemiologic studies and individuals. Applying the concept of LV mass (ECG ΣRV_{3-6}) interrelating with LV volume (chest[C] X-ray[XR] heart volume) an equation and nomogram was created that correlated angiographic EF in 59 patients with ischemia (EF range 13-79%, mean=50±17) using 3 independent variables: 1) CXR heart volume (cc/kg)=(heart length) (heart width) (lateral diameter)(.4); 2) Sum of ECG R waves=$\Sigma R(V_3-V_6)$; and 3) Inferior wall motion abnormality CODE 0, or 1 if a:Q in AV_F, or b:$\Sigma R<27$ and HV>11, or c:HV>17 and $\Sigma R<75$. Multiple linear regression formula is:
$EF=20.2 + 548.2\ HV^{-1.3} + 2.3\sqrt{\Sigma R_{V_{3-6}}} - 15.6$ (CODE) with a correlation, R=.86, SEE=8.86 and p<.001. This concept was then tested with 23 coronary artery disease (CAD), 15 dilated myopathy (DM), and 16 aortic valve disease (AVD) patients. The mean±SD predicted EF is compared to the measured EF with r=correlation coefficient, $\bar{\Delta}$=mean of ΣEFpred-EFmeas; SEE=standard estimate error:

	EFpred	EFmeas	EF range	r	P	SEE	$\bar{\Delta}$
CAD	36±13	36±16	11-65	.91	.001	6.7	-.13
DM	29±5	24±10	11-48	.75	.05	7.1	-4.7
AVD	49±15	52±19	25-80	.89	.001	9.5	3.1

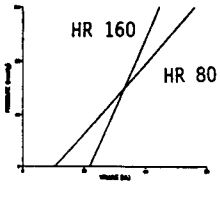
This method utilizes 2 simple tests routinely performed and separates patients with EF<50% vs >50% (sensitivity 94%, specificity 89%). Lack of expense stresses applicability as a screening tool for occult dysfunction.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #267
Systolic Function

INFLUENCE OF HEART RATE ON THE LEFT VENTRICULAR END-SYSTOLIC PRESSURE-VOLUME RELATION IN CONSCIOUS DOGS.

Gregory L. Freeman, M.D.,F.A.C.C., William C. Little, M.D.,F.A.C.C., Robert A. O'Rourke, M.D.,F.A.C.C., UTHSC and Audie Murphy V.A. Hospital, San Antonio, TX, 78284.

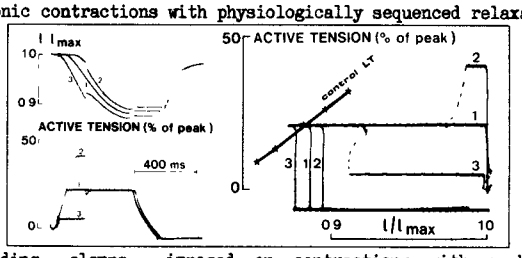
Prior studies on the influence of increased heart rate (HR) on left ventricular (LV) performance have had conflicting results. Accordingly, we studied the effects of atrial pacing on the end-systolic (ES) pressure (P) volume (V) relation (R) a relatively load-insensitive index of LV performance, in 6 chronically instrumented, conscious dogs. LVP was measured by a micromanometer catheter and LVV was determined from three ultrasonic orthogonal dimensions. Pressure was varied by caval occlusions at control (C) HR and 100, 120, 140, 160, 180, and 200 beats/min (BPM). The ESPVR is linear in every case (r=.96±.03, SD). E_{max}, the slope of the ESPVR, was directly and monotonically related to HR in every dog increasing to 221±69% of C at peak pacing rate (180 or 200 BPM, p<.005). V_o, the volume axis intercept of the ESPVR was also directly related to HR in every dog and showed a similar increase with pacing (255±135%, p<.01). This shift reduces stroke V from any end diastolic V, attenuating the benefits of enhanced contractility. We conclude that in conscious, autonomically intact dogs, increased HR has a dual effect on LV function. While contractility is increased, the ESPVR is shifted to the right, such that overall LV performance is relatively unchanged.



END-SHORTENING LENGTH-TENSION RELATION IN CAT PAPILLARY MUSCLE: DEPENDENCE ON LOADING HISTORY IN AFTERLOADED CONTRACTIONS

Thierry C. Gillebert, M.D., Stanislas U. Sys, Victor A. Claes and Dirk L. Brutsaert, M.D., F.A.C.C.
University of Antwerp, Antwerp, Belgium.

End-shortening length-tension (LT) values of afterloaded isotonic contractions yield a curvilinear relation. To compare contractions with different systolic history and equal end-shortening tension, load clamps of various magnitude were imposed at various times during shortening of afterloaded isotonic contractions with physiologically sequenced relaxation.



Unloading clamps, imposed on contractions with a higher afterload (contraction 2) resulted in a decreased extent of shortening, compared to the control contraction (contraction 1), hence in a shift to the right of the LT relation; later unloading clamps increased this shift. Loading clamps, imposed early on contractions with lower afterload (contraction 3) resulted in an increased extent of shortening, hence in a shift to the left of the LT relation; with later loading clamps, the control tension was not reached.

These data indicate that end-shortening LT relations depend on the history of the contractile events during systole, resulting in a family of LT curves instead of a single LT curve. They suggest that abnormal systolic loading profiles may influence LV pressure-volume relations.

DISSOCIATION BETWEEN REGIONAL MYOCARDIAL FUNCTION AND SUBENDOCARDIAL ST SEGMENT ELEVATION DURING EXERCISE-INDUCED ISCHEMIA WITHOUT AND WITH BETA BLOCKADE.

Maleah Grover-McKay, M.D. FACC, Masunori Matsuzaki, M.D., W. Scott Kemper M.S.E.E., John Ross, Jr, M.D., F.A.C.C., UCSD School of Medicine, La Jolla, California.

We examined the onset and resolution of ischemic changes using an electrical and a functional measure of myocardial ischemia. ST elevation on subendocardial electrograms and percent change in posterior wall thickness by sonomicrometry (%ΔWT) were measured in 9 conscious dogs with critical circumflex coronary artery stenosis (ameroid constrictor). The dogs performed control treadmill exercise (C) and a second identical exercise on the same day after atenolol, 1 mg/kg p.o. (A).

	Rest	EX:1min	2min	End	$\bar{p}$ EX:1min	5min	30 min
C ST(mm)	1.8	3.6	4.9*	5.8†	4.1†	1.8	1.6
C %ΔWT	27.9	5.4†	4.5†	5.0†	16.2†	20.9*	21.9
A ST(mm)	1.5	2.3	3.6*	4.3†	3.3†	1.6	1.5
A %ΔWT	26.2	8.3†	8.7†	9.1†	19.7	24.5	24.1

EX=exercise; $\bar{p}$ EX=post exercise; *p<.05; †p<.01; mean values
During both C and A, %ΔWT became abnormal prior to ST elevation. Following C, ST elevation returned to resting values prior to %ΔWT, but following A, %ΔWT returned to resting values prior to ST elevation. Transmural myocardial blood flow (MBF) in the ischemic region, normalized to the control region, decreased from 1.0 ± 0.1 at rest to 0.4 ± 0.2 during C (p<.01) and was significantly higher during A than C (0.7 ± 0.2; p<.01). We conclude that reduced MBF leads to rapid deterioration in %ΔWT which resolves slowly, and to slower onset of ST elevation which resolves quickly. After β-blockade the relative improvement in MBF to the ischemic region leads to more rapid improvement in %ΔWT but no change in the time of ST elevation resolution.

DEPRESSED SYSTOLIC MYOCARDIAL RESERVE IN DILATED CARDIOMYOPATHY

James D. Alderman, M.D., Raymond G. McKay, M.D., James J. Ferguson, M.D., Julian M. Aroesty, M.D., F.A.C.C., Henry D. Royal, M.D., William Grossman, M.D., F.A.C.C. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA.

Increases in heart rate (HR) result in enhanced systolic function due to a Treppe contractility effect, but quantification of this effect is not well-documented. Accordingly, 13 patients (pts) were examined during cardiac catheterization using 3 or more increasing atrial pacing rates with simultaneous measurement of high fidelity left ventricular (LV) micromanometer pressure and radionuclide ventriculography (RVG). Pressure-volume diagrams were constructed for each pacing level using LV pressure tracings and RVG volume curves. Group A included 5 cardiomyopathy (CMP) pts with normal coronary arteries (mean LV ejection fraction = 0.14). Group B included 8 pts with mild or no coronary artery disease (mean LV ejection fraction = 0.70).

All pts showed a variable leftward and downward shift of their pressure-volume diagrams. Changes in systolic function from baseline HR to HR+50 are shown below. (EF=LV Ejection Fraction, ESPVR=LV End-Systolic Pressure-Volume Ratio, LVEDV=LV End-Diastolic Volume, LVEDP=LV End-Diastolic Pressure).

	EF	dP/dt	ESPVR
CMP Group	0.14→0.11	+4%(876→916)	-14%(0.81→0.70)
Control Group	0.70→0.66	+18(1259→1760)	+20%(6.90→8.30)

	Relative LVEDV(%)	LVEDP(mmHg)
CMP Group	+14%(100→114)	-31%(26→18)
Control Group	-38%(100→62)	-50%(12→6)

Conclusion: Patients with dilated cardiomyopathy and depressed resting LV ejection fraction fail to exhibit increased contractility with tachycardia, suggesting loss of inotropic reserve.

IMPORTANCE OF THE ANTERIOR AND POSTERIOR MITRAL CHORDAE ON GLOBAL LEFT VENTRICULAR SYSTOLIC FUNCTION

David E. Hansen, M.D., Peter D. Cahill, M.D. William M. DeCampli, M.D., Ph.D., Donald C. Harrison, M.D., F.A.C.C., Cynthia Handen, B.A., Geraldine Derby, B.A., R. Scott Mitchell, M.D., D. Craig Miller, M.D., F.A.C.C. Stanford University, Stanford, CALIFORNIA

To determine the mechanical consequences of severing the anterior and posterior mitral leaflet chordae, 14 fentanyl-anesthetized dogs were studied during cardiopulmonary bypass. The slope of the LV peak isovolumic pressure-volume relation (Emax) was measured with a micromanometer inside a LV intracavitary balloon to assess global LV function independent of load. Balloon herniation was prevented by a disk reversibly secured to the mitral annulus. Compared to baseline determinations with the chordae intact, Emax decreased by 25% in 7 dogs (Group I) from 11.22±3.23 (±SD) to 8.44±3.29 mmHg/ml (p=0.02) after the chordal connections of the anterior leaflet were severed. Emax decreased similarly, from 13.13±4.27 to 9.80±3.13 mmHg/ml (p=0.02), in 7 dogs (Group II) in which the posterior leaflet connections were severed first. Severing the chordae of the remaining mitral leaflet caused additional decreases in Emax of 22% for Group I (p=0.10) and 33% for Group II (p=0.002). Since Emax decreased without discernible myocardial injury, these results challenge the concept that the slope of the peak isovolumic pressure-volume relation is solely dependent upon the contractile state of the ventricular myocardium. We conclude that both mitral chordae significantly (but unequally) influence global LV systolic function, which suggests that excision of the mitral apparatus at the time of MVR is detrimental to LV function. Chordae sparing surgery may be a rational alternative based upon better understanding of the complex mechanical interaction between the mitral valve and LV myocardium.

NORMALIZATION OF CARDIAC DYSFUNCTION INDUCED BY DIABETES BY REDUCTION OF THE CONCENTRATION OF EXOGENOUS FATTY ACID

Larry E. Fields, M.D. and Steven R. Bergmann, M.D., Ph.D. Washington University, St. Louis, MO

We previously demonstrated that in addition to hyperglycermia in vivo, alloxan-diabetic rabbits (n = 24) exhibit higher plasma free fatty acid (FA) levels than controls (n = 18) (333 ± 70 vs 116 ± 22 μM, mean ± S.E., $p < .05$) and that hearts isolated from the diabetic animals exhibit depressed LV function. To determine whether the LV dysfunction associated with diabetes reflects increased susceptibility to deleterious effects of high concentrations of exogenous FA, we characterized hearts isolated from 10 normal and 6 diabetic rabbits perfused at constant flow at 37°C with erythrocyte-enriched modified Krebs-Henseleit media with a low concentration of palmitate (.06 mM bound to 0.4 mM albumin) and hearts isolated from 22 normal and 24 diabetic animals perfused with high FA (0.4 mM with equimolar albumin). LV systolic pressure, dP/dt, and pressure-time index at a fixed EDP and HR were decreased by > 40% in hearts from diabetics perfused with high FA ($p < .01$ vs. controls). In contrast, LV performance did not differ from that in controls when hearts from diabetic rabbits were perfused with low FA. Perfusion of diabetic hearts with low FA was associated with lower tissue FA (149 ± 18 nmol/g) and triacylglycerol (TAG) (3.8 ± 0.5 μmol/g) compared to diabetic hearts perfused with high FA (FA: 495 ± 70 nmol/g; TAG: 15.6 ± 3.1 μmol/g; $p < .05$ for each). Hyperlipemia in vivo as well as LV performance and myocardial lipid content were normalized as well by insulin given over 10 days (n = 7). Thus, impaired LV performance in hearts from diabetic animals appears to reflect increased susceptibility to the deleterious effects of exogenous FA, suggesting that reduction of hyperlipemia may mitigate cardiac dysfunction in diabetics.

Thursday, March 13, 1986
8:30AM–10:00AM, Room #268
Modulation of Arrhythmias with Adrenergic and Calcium Blocking Agents

DOES VERAPAMIL INCREASE OR DECREASE VAGAL EFFECT ON ATRIOVENTRICULAR NODAL CONDUCTION?

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Possible direct vagolytic effects of verapamil (V) on the sinus and atrioventricular (AV) nodes were recently reported. To evaluate the interaction of V and vagus (VG) the effect of postganglionic vagal stimulation (PGVS) on AV nodal conduction was studied in 16 isolated atrial-AV nodal rabbit preparations before and after V (10^{-8} to 10^{-6} M) at a constant drive cycle length (400-500 msec). Microelectrode recordings showed that PGVS produced hyperpolarization and subsequent decrease of dv/dt and amplitude of slow-channel-dependent action potentials in the N region of the node. V also decreased dv/dt and amplitude of these action potentials, but did not produce hyperpolarization or change of the take-off potential. In combination, V and PGVS consistently accentuated the depression of AV nodal conduction ($p < 0.01$). For example, maximal increase in conduction time with PGVS was 30% in control, 40% after V (5×10^{-8} M) and 61% after V (10^{-7} M). Also, AV nodal block was observed with PGVS plus V while neither intervention alone resulted in AV block. The direct effect of V on PGVS-induced maximum hyperpolarization was not significant, although the vagal-induced rebound, responsible for increased diastolic depolarization after PGVS, was accentuated by V. Moreover, action potentials showed greater depression of dv/dt when PGVS was introduced after V, even though the cells fired from similar take-off potentials. Thus, the combined effect of V and PGVS on AV nodal conduction was additive and could be explained by increased sensitivity of V-depressed slow channel currents in response to vagal-induced hyperpolarization, resulting in conduction delay and block. The enhanced negative dromotropic action of vagal stimulation on the AV node after verapamil argues against direct vagolytic properties of this drug.

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VERAPAMIL, DILTIAZEM AND NIFEDIPINE: DIFFERENT EFFECTS ON THE RABBIT SINUS NODE

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Medical Hospital I, University of Munich, FRG

In humans, the direct effects of verapamil (V), diltiazem (D) and nifedipine (N) on sinus node function are concealed by reflex mechanisms. We studied the direct action of V, D and N (1 to 30 x 10^{-7} M) on the isolated rabbit sinus node (n=46) by multiple intracellular recordings. The increase of cycle length (CL) after drug application differed substantially: N caused severe bradycardia already in low doses inducing sinus arrest with 24 x 10^{-7} M at most. The bradycardic effect of V was comparable to N at molar concentrations four times higher. Increase of CL under D was moderate with sinus arrest in only 2/16 cases. Corrected sinus node recovery time increased with V and D, but was unaffected with N.
Each drug decreased effective atrial refractory period by about 10% ($p < 0.01$).
The transmembrane potential of dominant fibers revealed different mechanisms of the bradycardic action: V caused a shift of the take-off potential and increase of action potential duration, phase 4 remained unchanged. D slowed diastolic depolarization, but did not alter action potential duration. N slowed phase 4 and repolarization.
All drugs (10^{-6} M) decreased the total transmembrane potential by 16 mV ± 15. Pacemaker shifts in caudal direction occurred with V and N, not with D.
Our results reveal differences of extent and cellular mechanism of the negative chronotropic actions of V, D and N on the isolated sinus node.

EFFECTS OF d- AND l-SOTALOL ON ATRIAL ELECTROPHYSIOLOGY AND ATRIAL FLUTTER INDUCED IN CONSCIOUS DOGS WITH STERILE PERICARDITIS.

Ken Okumura, M.D., Augusto Scalabrini, M.D., Albert L. Waldo, M.D., F.A.C.C., University of Alabama at Birmingham, Birmingham, Alabama.

Agents which prolong the atrial effective refractory period (ERP) have been shown to slow or interrupt atrial flutter. We studied the effects of d-sotalol (d-S), said mainly to prolong ERP, and l-sotalol (l-S), said mainly to be a β-blocker, on stable, reentrant atrial flutter (AFl) induced in conscious dogs with sterile pericarditis. d-S and l-S (2 mg/kg) were given intravenously during AFl in 7 and 8 dogs, respectively. Their effects on the flutter cycle length (AFl-CL) and ventricular rate (VR) during AFl and also on the sinus cycle length (SCL), atrial excitability threshold, atrial ERP and intraatrial conduction time (CT) were noted. Atrial excitability threshold, ERP and CT were measured during atrial pacing at 150 bpm. 3 pairs of wire electrodes placed at selected atrial sites were used for pacing and recording and for AFl induction. Results: Neither drug affected atrial excitability threshold or CT.

	Control	d-S	Control	l-S
SCL(ms)	454±21	536±26*	453±48	633±112**
ERP(ms)	133±13	156±15*	133±14	163±25*
AFl-CL(ms)	132±16	150±16*	124±12	143±19+
VR(bpm)	212±30	176±41**	206±40	158±32+

(mean±SD. *P<.001, **P<.005, +P<.01 vs Control)

Both d-S and l-S prolonged AFl-CL in all dogs. After first causing prolongation of AFl-CL, d-S interrupted AFl in 6/7 dogs at a mean of 4 min 37 sec after administration and l-S interrupted it in 8/8 at a mean of 2 min 38 sec. Isoproterenol (2 mcg bolus injection) shortened post d-S SCL by 17±6% but post l-S SCL only by 2±2%. Conclusions: d-S shows class III antiarrhythmic effects with little β-blocking effect, while l-S shows both. d-S and l-S are both equally effective in interrupting AFl, presumably by prolonging atrial ERP.

EVIDENCE FOR MODULATED RECEPTOR EFFECTS OF CALCIUM ANTAGONISTS IN VIVO.

Stanley Nattel, M.D., F.A.C.C., Mario Talajic, M.D., and Scott Beau, McGill University, Montreal, Canada

The modulated receptor hypothesis suggests that calcium antagonists should produce interval-dependent calcium channel blockade. To evaluate this possibility in vivo, loading and maintenance infusions of diltiazem (D) and verapamil (V) were used to study drug effects at 4 stable concentrations in anesthetized autonomically blocked dogs. Programmed stimulation was applied to evaluate the interval dependence of AV conduction time (AVCT) prior to and after drug infusion. AVCT of early premature beats increased under control conditions with a time constant (t) of 79±20 msec (M±SD). D and V did not alter the interval dependence of AVCT slowing for very early premature beats, but resulted in two additional time - dependent phases of conduction slowing with t averaging 2.5±.8 and 11.3±3.1 sec for D, and 2.4±1.4 and 30.1±11.9 sec for V. While AVCT and AV node ERP (AVERP) were constant over a wide range of heart rates under control conditions, increases in AVCT and AVERP resulting from D and V were greatly enhanced by increases in heart rate over the physiologic range, and substantially reduced with pauses or bradycardia. We conclude that the effects of D and V in vivo are consistent with predictions from the modulated receptor hypothesis and previous in vitro work. These results have potentially important implications for understanding the effects of calcium blocking drugs on supraventricular tachyarrhythmias.

DELETERIOUS EFFECTS OF BRETYLIUM ON HEMODYNAMIC RECOVERY FROM VENTRICULAR FIBRILLATION.

David E. Euler, Ph.D., Therese W. Zeman, M.D., Michael E. Wallock, B.S., and Patrick J. Scanlon, M.D., F.A.C.C., Loyola University Medical Center, Maywood, Illinois

To study the effects of bretylium (B) on the restoration of circulatory function after resuscitation from ventricular fibrillation (VF), closed-chest anesthetized dogs were fibrillated by applying 60 Hz current to the right ventricle via a transvenous catheter. After one minute of VF, defibrillation was achieved by a single 150 watt-second DC shock. After one control episode of VF, 16 dogs received an intravenous bolus of B (10 mg/kg). A second episode of VF was studied in eight dogs three minutes after B and in eight dogs four hours after B. Prior to B mean arterial blood pressure spontaneously recovered to exceed 200 mg Hg by two minutes after defibrillation in all 16 dogs. However, after B, 13/16 dogs were in electromechanical dissociation two minutes after defibrillation ($p \leq 0.001$). Despite external chest compression, epinephrine and sodium bicarbonate, a stable blood pressure could not be restored in 6/16 dogs. The duration of exposure to B (three min. vs. four hours) did not significantly influence the degree or rate of hemodynamic recovery following defibrillation. In eight dogs treated with saline instead of B, there was spontaneous recovery of normal hemodynamic function within two minutes after defibrillation in all dogs. Also, a B analogue lacking sympathetic influences, clofilium (2 mg/kg), did not alter the pattern of hemodynamic recovery after one minute of fibrillation in 5/5 dogs. The results suggest that the effects of B on the sympathetic nervous system may profoundly influence the outcome of cardiac resuscitation from VF.

MECHANISM OF PREVENTION OF SUDDEN DEATH BY NADOLOL: DIFFERENTIAL ACTIONS UPON TRIGGERS AND ARRHYTHMIA SUBSTRATE

Eugene Patterson, Ph.D., Benjamin J. Scherlag, Ph.D., F.A.C.C., and Ralph Lazzara, M.D., F.A.C.C. University of Oklahoma Health Sciences Center and VA Medical Center, Oklahoma City, OK.

Holter monitoring and provocative ventricular pacing (PVP) were used to evaluate control and nadolol treatment groups, 6-24 hr after left anterior descending coronary artery ligation (CAL) in the dog. The control group (N=20) developed ventricular couplets and triplets (>270 bpm), 6-24 hr after CAL. Seven dogs developed spontaneous sustained monomorphic ventricular tachycardia (SMVT) (421±12 bpm) at 13±2 hr. The SMVT was present for 38±8 sec before ventricular fibrillation developed. VP (345±11 bpm) produced SMVT (378±12 bpm) in 9 of 13 surviving animals at 24 hr. Nadolol (1 mg/kg, N=19), administered 6 hr after CAL, prevented spontaneous SMVT in the 6-24 hr period (0%; p=0.005) and increased survival at 24 hr (95%; p=0.0047). Nadolol failed to prevent SMVT (88%; 365±12 bpm) produced by PVP (356±12 bpm) at 24 hr and failed to alter infarct mass (27±12 vs 29±2 gm). Both the PVP rate to induce SMVT and the SMVT rate were not different in control and drug treatment groups. The drug, however, lowered both the rate (241±8 vs 328±8 bpm, p=0.0001) and the incidence (8±6 bs 198±61/hr, p=0.004) of rapid ventricular triplets in the 6-24 hr period. The data suggest that nadolol prevents spontaneous SMVT by selectively suppressing the arrhythmia trigger (rapid ventricular triplets) without altering the underlying without altering the underlying substrate capable of sustained myocardial reentry.

POST-SYNAPTIC ALPHA$_2$-ADRENERGIC RECEPTORS MEDIATE CORONARY VASOCONSTRICTION DURING SYMPATHETIC NERVE STIMULATION.

Xue-Zheng Dai, M.D., D.G. Chen, M.D., Robert J. Bache, M.D., F.A.C.C.
University of Minnesota, Minneapolis, Minnesota.

This study examined the relative importance of post-synaptic α_1 and α_2 activity in mediating coronary vasoconstriction during sympathetic neural stimulation. The left circumflex coronary artery was cannulated and blood perfused with a pump at a constant flow rate in 8 open chest vagotomized dogs; β-adrenergic blockade was produced with propranolol, 1 mg/kg, i.v. Coronary vasomotor activity was assessed from changes in coronary perfusion pressure in response to electrical stimulation of the decentralized inferior cardiac nerve (NS) and intracoronary norepinephrine (NE) (0.03 µg/kg bolus dosages) during baseline conditions, after α_1-blockade with prazosin, 300 µg/kg i.v. (PRAZ), and after the addition of α_2-adrenergic blockade with idozoxan, 5 µg/kg/min intracoronary (IDO). Coronary perfusion pressure (mmHg) during control conditions (CON) and the response to NS AND NE are listed below.

	CORONARY PERFUSION PRESSURE (mm Hg)					
	CON	NS	Δ	CON	NE	Δ
Baseline	73±7	94± 9†	21±3	71±4	92±5†	21±1
PRAZ	67±9	90±13†	22±4	57±8*	78±8†	21±2
IDO	54±9*	54±10*	1±1*	58±9*	58±9*	0±1*

*P<0.05 vs. Baseline. †P<0.05 vs. CON

The increased coronary perfusion pressure was not significantly altered by PRAZ but was markedly decreased after IDO. These data indicate that coronary vasoconstriction in response to cardiac NS and exogenous NE is mediated principally by post-synaptic α_2-adrenergic mechanisms.

Thursday, March 13, 1986
10:30AM–12:00NOON, Room #268
Coronary Vasomotion—Flow and Function

ROLE OF CORONARY ENDOTHELIUM IN CONSTRICTION AND RELAXATION.

Richard J. Bing, M.D. and Maythem Saeed, Ph.D., Huntington Medical Research Institutes, Huntington Memorial Hospital, Pasadena, Calfornia

The protective action of the endothelium in isolated aortic rings against vasoconstriction has been demonstrated by Furchgott. Using rabbit hearts in supported working heart preparations perfused with FC-43, a perfluorocarbon, we demonstrated the presence of this protective factor (EDRF, endothelial derived relaxing factor) in intact coronary arteries. Cardiac function, coronary flow and myocardial oxygen consumption and changes in internal diameter of epicardial coronary arteries were measured. The latter was accomplished by means of color arteriography (injection of patent blue dye in the left atrium followed by gated photography). Diameter of coronary arteries was determined on projected slide. We demonstrated the presence of EDRF in intact coronary arteries with preserved endothelium. Activated platelets and acetylcholine failed to constrict these vessels. Since EDRF activates cGMP, we measured the vasodilatory effect of a substituted cyclophosphate. In aortic rings, 8-Br-cGMP (10^{-5} M) caused more relaxation in endothelial deprived preparation. In denuded arteries, dose response curves with 8-Br-cGMP (10^{-8} to 10^{-4} M) shifted to the left. In intact coronary arteries (perfusion model), 8-Br-cGMP (10^{-4} M) blocked coronary vasoconstriction induced by 0.1 units of Pitressin (decrease in coronary flow 50%, decline in internal diameter of coronary artery with Pitressin from 0.38 ± 0.02 mm to 0.23 ± 0.03 mm; after 8-Br-cGMP: from 0.40 ± 0.02 to 0.36 ± 0.02). It is concluded 1) that EDRF is protective in intact coronary arteries and 2) 8-Br-cGMP prevents coronary artery constriction, particularly in arteries deprived of endothelium.

NEUROPEPTIDE Y CORONARY VASOCONSTRICTION IS INDEPENDENT ON ADRENERGIC AND MUSCARINIC RECEPTORS.

Jose M. Brum, M.D., Ronald Dotson, B.S., Lair G. Ribeiro, M.D., Alfred A. Bove, M.D., Ph.D., F.A.C.C., Geetha Ghai, Ph.D., Mayo Clinic/Ciba Geigy, Rochester, MN/ Summit, NJ.

Neuropeptide Y (NPY) is a neurotransmitter polypeptide found in adrenergic nerves in the epicardial coronary arteries, whose action is vasoconstriction. In the present experiment the interaction of NPY with adrenergic and muscarinic receptors was studied in isolated rabbit coronary arteries. The arteries were perfused in a 20 ml chamber by a constant flow perfusion system with oxygenated KrebsHenseleit solution at 37°C. Changes in perfusion pressure reflected changes in vessel resistance. NPY effects were compared with control perfusion pressure and with the increase in pressure produced by prostaglandin (PG) $F_{2\alpha}$ 10^{-5} M. NPY dose-response curves varying from 10^{-12}M to 10^{-8} M were obtained in the presence of phentolamine (10^{-5} M), propranolol (10^{-5} M), and atropine (10^{-6}M). Increase in perfusion pressure by $PGF_{2\alpha}$ (35+8.9 mmHg) was larger than the response to NPY up to 10^{-9} M (9.2±4.6 mmHg). However, NPY at 10^{-8} M (44.6±16.2 mmHg) produced signficant coronary constriction that did not differ from the constrictor effect of $PGF_{2\alpha}$ 10^{-5} M. Adrenergic alpha and beta and cholinergic muscarinic blockade did not significantly inhibit the vasoconstrictor response to NPY. The presence of NPY in the coronary autonomic nerves and its coronary constrictor action independent of adrenergic and cholinergic receptors suggests an important role in coronary vasoregulatory mechanisms. This mediator might be a contributing factor in the pathophysiology of the coronary artery spasm.

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CALCITONIN GENE RELATED PEPTIDE IS A POTENT CORONARY ARTERY DILATOR.

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The localization of neuropeptides in the cardiovascular system has suggested a physiological role of peptidergic nerves in cardiovascular regulation. Calcitonin Gene Related Peptide (CGRP) is produced by post-transcriptional modification of the calcitonin gene mRNA. It circulates in man and has been identified in the rat heart particularly in the coronary arteries, and appears to be a potent systemic vasodilator in man. We studied the effect on coronary artery diameter of infusion of saline as control followed by CGRP in incremental doses into the left coronary artery. Six patients were examined during routine angiography. Four patients had atypical chest pain and normal coronary arteries and 2 had variant angina with coronary spasm superimposed on non-critical lesions. The maximum dose of 200 ng/min for 5 minutes was 1/20th of the maximum systemic dose reported and caused no systemic effect other than mild facial flushing. Coronary arteriography was repeated after each infusion period and epicardial vessel diameter measured manually and using a CAAS computer system. No effect of saline was found but a dose dependent increase in arterial diameter occurred during CGRP infusion. The maximum increase in proximal circumflex, and in proximal, mid and distal left anterior descending artery diameter was 35%, 20%, 21% and 83%, respectively with a 32% increase at the site of the two atheromatous lesions. Intracoronary injection of 1.5 ug CGRP relieved ergometrine-induced pain, ST elevation and coronary spasm in 2 patients, though prior infusion had not prevented the spasm.
The demonstration of dilatation of coronary arteries as well as vascular localization suggests that CGRP could have a role in the control of coronary smooth muscle tone.

EPICARDIAL CORONARY ENDOTHELIAL DAMAGE PRODUCED BY CHRONIC SPASM IN DOGS.

Alfred A. Bove, M.D., Ph.D., FACC, Jose M. Brum, M.D, Qian Sufan, M.D. Mayo Clinic, Rochester, MN.

We have recently observed increased sensitivity to serotonin vasoconstriction in endothelial damaged epicardial coronary artery segments in vivo. In vitro studies have demonstrated that acute vasoconstriction can produce areas of endothelial injury in large conducting arteries. In this study, we examined the effects of focal, chronic left anterior descending epicardial coronary constriction in 6 dogs given a 2 week perivascular ergonovine (ergo) infusion (120 ug/hr) with a surgically implanted perivascular catheter connected to an implanted osmotic minipump. Focal constriction with ergo, by quantitative coronary angiography, averaged 19.2% cross sectional reduction in 5 treated dogs. In 3 saline controls, area increased 12.3% ($p<.01$) following angiographic study, the heart was removed, the arteries flushed with saline, and perfusion fixed with 1.5% gluteraldehyde at 100 mm Hg for 4 hours. The arteries were dissected, mounted and prepared for scanning electron-microscopy. In all ergo constricted segments the endothelium demonstrated disruption, and overlapping in a shingle-like arrangement not found in untreated arteries or in saline treated controls. These in vivo data confirm in vitro studies demonstrating that focal coronary spasm causes endothelial damage. Spasm induced endothelial damage may be an initiating event in intracoronary thrombus formation, and in the production of fixed coronary narrowing.

REGIONAL ALPHA 2 BLOCKADE IMPROVES FUNCTION AND FLOW IN THE ISCHEMIC DOG MYOCARDIUM DURING EXERCISE.

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Sympathetic vasoconstriction mediated by postsynaptic alpha receptors could aggravate myocardial ischemia during exercise. To investigate this question, we carried out experiments in conscious dogs instrumented with an intracoronary (IC) catheter and a hydraulic occluder on the circumflex coronary artery. Systolic wall thickening (%WTH, sonomicrometry) and regional myocardial blood flow (MBF, radiolabeled microspheres) were assessed. After beta-blockade (propranolol, 0.8mg/kg iv.), treadmill exercise (5mph, 5% elevation) initially increased posterior wall (PW) %WTH, but while running continued acute coronary stenosis then decreased PW-%WTH from 21.0 $\pm$ 1.8 (S.D.) to 5.1 $\pm$ 1.6. With steady state running MBF was measured and the selective alpha 2 blocker idazoxan was given IC (80 µg/kg). PW-%WTH promptly improved from 5.1 $\pm$ 1.6 to 10.8 $\pm$ 2.8 ($n=5$, $p<0.028$) without changing anterior wall %WTH, heart rate or arterial pressure. In every experiment the PW subendocardial MBF improved (0.17 $\pm$ 0.05 vs 0.45 $\pm$ 0.30ml/min/g, $n=5$), and the PW endo/epi ratio increased markedly (0.22 $\pm$ 0.09 vs 0.60 $\pm$ 0.41, $n=5$). In the same model, the selective alpha 1 blocker prazosin (20 µg/kg) diminished PW function and MBF and reduced arterial pressure. We conclude that in the presence of beta blockade, significant postjunctional alpha 2 coronary vasoconstriction is induced by exercise even with severe ischemia. Regional alpha 2 blockade can markedly reduce ischemia by attenuating sympathetic vasoconstriction. This response may carry clinical implications for patients on beta blockers and open a new approach to therapy.